THE FEASIBILTY OF USING HEART RATE VARIABILITY TO DETECT DISTRESS

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by

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Statement of Originality and Authorship:

This work is original and unless otherwise acknowledged in the text or by references, has been performed by myself. Parts of this work have been published during the development of the research.

This work was performed in the Department of Engineering at the University of Leicester, during the period between September 2000 and July 2003 (supported by an EPSRC scholarship No. 00307094).

None of this work has been submitted for another degree in this, or any other university.

Signed,

Anita Boardman

Date:

31st July 2003

The feasibility of using heart rate variability to detect distress

Anita Boardman

The correct identification of asphyxial distress occurring during labour is very difficult. The objective of this work is to look at the feasibility of using heart rate variability analysis, which has been used previously in assessing the function of the autonomic nervous system, as a method of improving discrimination between those fetuses suffering distress and those not.

Analysis of the variability of the heart rate can be undertaken in both the time and the frequency domains. In order to perform frequency domain analysis for this application it is necessary to use short frames of data: an autoregressive analysis was used and the model order prediction criteria of Akaike, Parzen and Rissanen tested for these data. The model orders are underestimated using these criteria and these low model orders produce smoothed spectral responses. It was found to be better to specify an arbitrary model order and here this was set to at least $p = 16$.

Heart rate variability analysis was applied to data acquired from rats who had undergone asphyxia for set durations of up to 7 minutes. From analysis in both the time and frequency domain, it was possible to clearly identify the occurrence of the injury. Further correlations were made between these results, pH levels and neurological assessments for the different durations of asphyxia. It was found that during and following the injury, the pH and the heart rate decrease as expected, but the overall change in heart rate variability was much more pronounced. Some interesting results were also found for the shorter durations of asphyxia which will be looked at.

Fetal heart rate data was collected before and during labour in normal patients and variability analysis of the heart rate was performed. The acquisition of heart rate data using Doppler ultrasound is discussed and comparisons made between heart rate data acquired non-invasively using Doppler ultrasound and that acquired invasively using the scalp electrode during labour. It was found that providing the ultrasound signals did not suffer greatly from noise, a reasonable comparison of beat-to-beat intervals and the time domain measure of heart rate variability was possible. The application of these results is discussed.

In conclusion, it has been found that it is feasible to detect asphyxial distress in rats using the standard deviation of 30 second intervals of heart beats. It has also been possible to collect fetal heart rate data and perform a similar heart rate variability analysis however further work needs to be undertaken to find out if this is predictive of distress in the fetus during labour.

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Table of Contents

1.0 Introduction

The Confidential Enquiry into Stillbirths and Deaths in Infancy, reported a mortality rate of 0.62 per 1000 births in England, Wales and Northern Ireland in 1999 (CESDI 1999). While some deaths are unavoidable, it is thought that more can be done to reduce this level of mortality.

Labour is the most dangerous event of life (Gibb and Arulkumaran 1997), it is therefore unsurprising that things can and do go wrong. Distress, which occurs when there is a reduction in oxygen supply to the fetus, ultimately can cause a variety of health problems, which include deafness, learning difficulties, cerebral palsy, brain damage and death (Robertson *et al.* 1993). It is thought that in some cases, if not all, this type of damage could and should be prevented. In order to do this, various methods of distress detection are available, the most popular include testing pH levels of the fetal blood and monitoring the fetal heart rate. In the early 1960s electronic fetal heart rate monitoring was introduced as the method which would reduce all cases of fetal damage and death to practically zero: this has not happened (Parer and King 2000).

This study is concerned with these electronic fetal heart rate records. Knowledge regarding the health of a patient can be obtained from visual analysis of the ECG and some heart problems are identified in this way. Looking at the heart rate in its simplest form, bouts of tachycardia or bradycardia can be noted along with the heart's variability. The influencing factors controlling the heart rate are complicated; they come from mechanical influences such as the action of the heart muscle and from the autonomic nervous system, which modulates the firing of the heart's pacemaker. It is possible to find out information about the health of the autonomic nervous system by analysing the heart rate.

1.1 What is being studied?

The first part of the work looks specifically at heart rate variability analysis in healthy adults. A number of methods for performing power spectral analysis have been suggested which produce results applicable in different circumstances. Power spectral analysis is particularly useful in showing the different frequency components present in the heart rate signal and Fourier analysis has commonly been used for this. However, when analysing short segments of data this type of analysis is not as effective due to the windowing constraints of Fourier analysis. Autoregressive power spectral analysis is known for its higher resolution for short frames of data and it is thought that this will produce improved results. The main problem in using autoregressive power spectrum analysis is that an order must be chosen which dictates the level of complexity of the autoregressive analysis. Here, criteria put forward by other researchers for the selection of model order are tested for analysis of heart rate variability signals from healthy adults; the results achieved will be useful for the rest of the work undertaken.

Returning to the problem of detecting fetal distress, a number of techniques have been tested to try to improve detection of asphyxial distress, but it is thought that the sensitivity and specificity of these methods could be improved. When there is a deficit in oxygen level in the blood stream, the heart rate decreases, to conserve the amount of oxygen left in the system. It is this principle which the electronic fetal heart rate monitors employ to aid detection of distress. However a decrease in heart rate also occurs during rest compared with activity so the ability to differentiate between different levels of activity and the occurrence of asphyxia is required. As already noted, the heart rate trace produces some information about the status of the patient but the variability of the heart rate may prove to be more informative. Before moving to test the validity of this proposal in the delivery room, the heart rate and heart rate variability of adult rats asphyxiated for set lengths of time was investigated to discover whether a measure of heart rate variability is superior to using just heart rate to detect asphyxia. The pH of the fetal blood is another indicator used in the delivery suite; the results from the heart rate variability analysis will be compared with pH levels using the animal model.

Finally the results from these two sections of work are applied to the original problem of detecting fetal distress during labour. The electronic fetal heart rate monitors are able to collect data in two ways: non-invasively, using a Doppler ultrasound transducer or invasively using a fetal scalp electrode. Non-invasive monitoring is often easier to set up and can be used in a greater number of circumstances. The Doppler transducer is placed on the skin's surface and aimed at a blood vessel. It transmits an audio signal which is scattered by particles in the blood and when returned to the receiver a change in frequency of the returning signal can be found. By tracking the fastest flowing blood cells an envelope signal can be derived which allows heart beats to be identified. Beat-to-beat intervals can be found from this envelope signal in two ways and this will be compared with the envelope signal produced by the HP8040A cardiotocograph.

The scalp electrode provides a definitive record of ECG data; heart rate variability derived from this and the Doppler heart rate data will be compared to determine whether the Doppler record, if analysed correctly, can be as accurate as the ECG record. The data will be collected from normal patients and the heart rate variability trace will be looked at.

1.2 Why is this being studied?

The overall motivation for this study has already been given: improving the monitoring of fetuses who may suffer distress during labour so that this is detected at the earliest opportunity, thus allowing the fetus the best possible chance of a healthy life.

There are other factors too which would benefit from an improved monitoring system. Missing vital information regarding the deteriorating health of a fetus which then leads to catastrophe can land the NHS with a bill for litigation: current estimates show costs associated with litigation from failure to respond to abnormal traces to be £100 million per year (RCOG 2001a).

Misinterpreting results can also lead to needless interventions: the Caesarean section rate in England has almost doubled in ten years to 21.3% of all deliveries (RCOG 2001b); the World Health Organisation's recommendation is for a rate of 10-15% to be the maximum (RCOG 2001b).

Caesarean section involves major abdominal surgery, puts both mother and baby at risk and complications which may occur, include hysterectomy, postnatal depression and death. It has been found that 87% of mothers suffer some morbidity following the surgery (RCOG 2001b). In terms of resources, in the mid 1990s it was estimated that it costs £760 more to perform a Caesarean section than a vaginal delivery (Health Committee report 2003) and whereas in normal labour one midwife is assigned to each mother, three midwives are needed for an operative delivery; this takes valuable resources away from other patients.

In 22.0% of mothers in England and Wales urged to undergo a Caesarean section, presumed fetal compromise, intrauterine growth retardation or an abnormal cardiotocograph recording was the second most frequently noted reason for intervention (the first being a previous Caesarean section) (Health Committee report 2003); which again highlights the dilemma of whether all cases of fetal distress identified are truly indicating a problem.

A final point concerns the increase in use of automated analysis for patient data. Currently in the UK there are staff shortages throughout the medical profession which leads to greater burdens on those currently employed. It has also been noted that care on a delivery ward during the day is safer than during the night when staffing is less (Stewart *et al.* 1998, Heller *et al.* 2000). It has been stated by those working in the field that the implementation of a system which does not require a lengthy manual analysis would be beneficial (Waugh 2002).

1.3 Organisation of thesis

The factors which control the heart rate are looked at in chapter 2. The motivation for this work is clear: any improvements made to fetal monitoring during labour would be welcomed. The current methods of monitoring available and the problems associated with their use are presented and discussed in chapter 3. The usefulness of power spectral analysis of heart rate variability has been touched on and more background to this, as well as the selection of model order for the use of short segments of data in autoregressive analysis is given in chapter 4. This is useful for looking at the change in power spectra during asphyxia, which the following two chapters will cover.

Before entering the clinical situation it is very valuable to be able to test the algorithm in a situation where asphyxia is known to be occurring and for different degrees of injury. Obviously this is not possible in humans, hence the use of rats: this work is presented in chapter 5.

Two methods can be used to derive the Doppler envelope signal from the Doppler audio signal and these will be looked at in chapter 6.

The algorithm for finding heart rate variability is applied to fetal heart rate data in chapter 7. Comparisons of the results obtained using heart rate data derived from ultrasound blood flow and scalp ECG data are also made. Chapter 8 brings together the work covered in the thesis and gives some conclusions and suggestions for future work.

2.0 The control of the heart

2.1 Introduction

The function of the heart is to pump blood, supplying vital nutrients such as oxygen to every part of the body. The rate which the heart pumps blood at is dependent on circumstances. For example, the heart rate increases during exercise as more blood is required by those muscles doing work, whereas during sleep the heart rate decreases. In this chapter, the mechanisms which control the human heart are looked at and the derivation of information from the variation in heart rate is also introduced.

The cardiac output of the heart, the amount of blood pumped around the body per minute, depends on the heart rate and the stroke volume. Heart rate is governed by pacemaker activity which is regulated by the autonomic nervous system. Stroke volume depends on myocardial performance arising from both intrinsic and extrinsic factors. Both of these factors will now be discussed (Berne and Levy 1997).

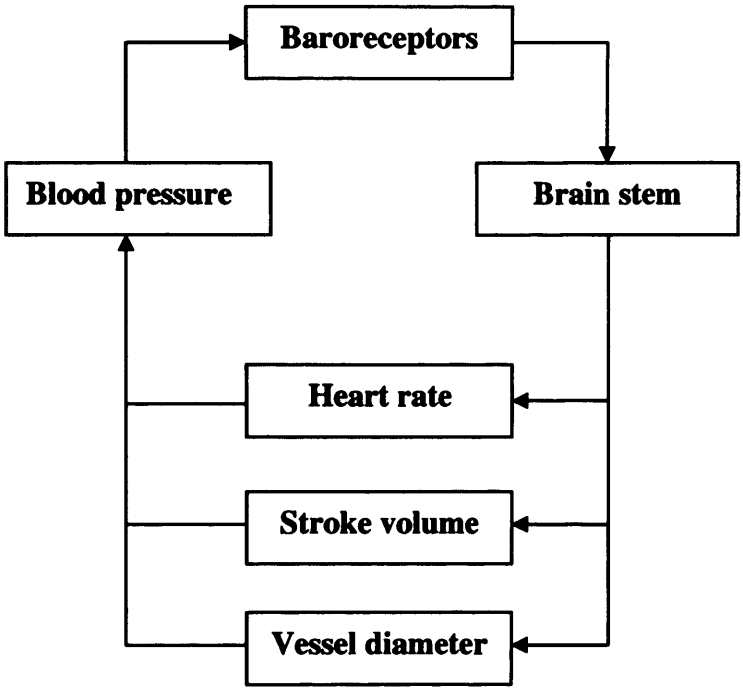


Figure 2.1: *Feedback control of blood pressure which influences stroke volume and heart rate. Adapted from Ganong (2001).*

2.2 Control of the heart rate: The autonomic nervous system

The vasomotor centre (figure 2.2) controls the activity of the heart and the vasoconstrictor system by transmitting signals through the sympathetic and parasympathetic nervous systems which make up the autonomic nervous system (Guyton and Hall 1997).

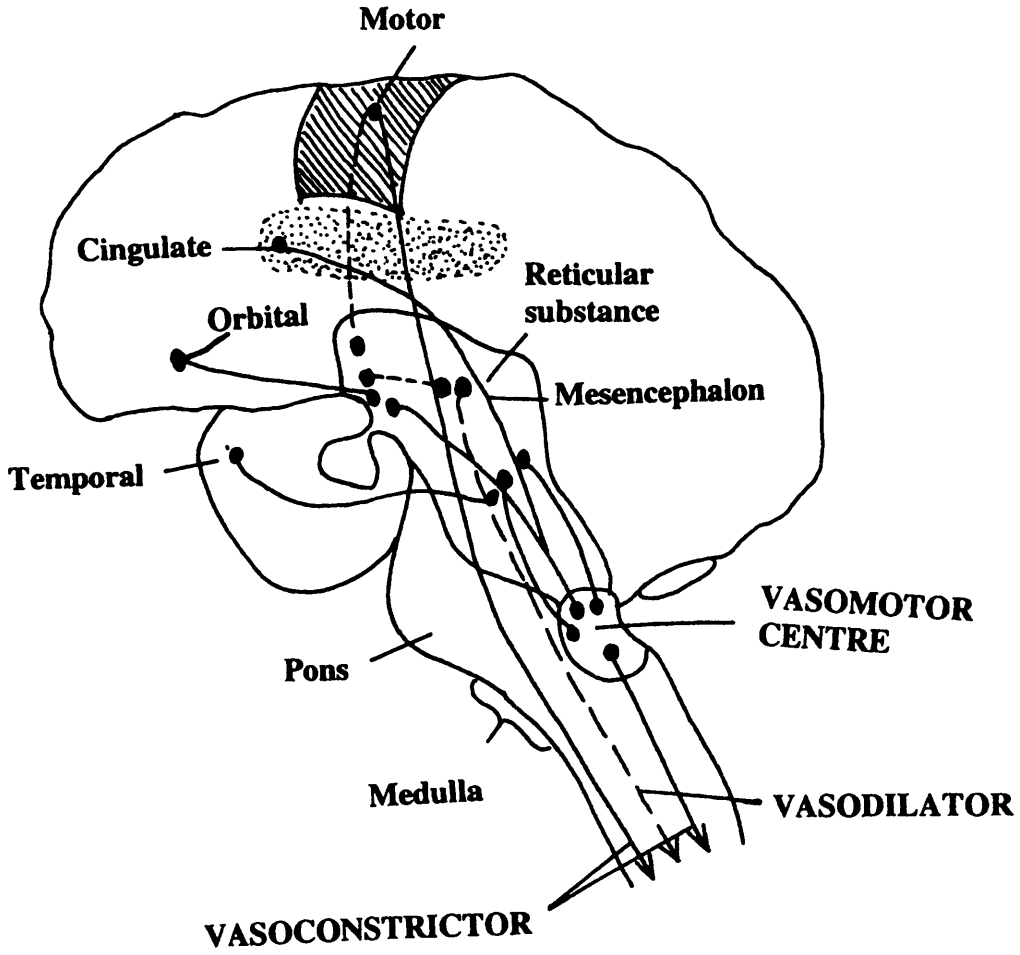


Figure 2.2: *Diagram of areas of the brain which play a part in nervous regulation of the circulation. Adapted from Guyton and Hall (1997).*

The sympathetic system plays a large part in regulating the circulation also and both systems act together in a reciprocal manner in regulating heart rate. Impulses transmitted through the sympathetic nerves cause the heart rate to increase whereas impulses transmitted through the vagus nerves cause the heart rate to decrease as the systems act together in influencing the sino-atrial (SA) node (Berne and Levy 1997, Guyton and Hall 1997). The right and left vagal fibres are also distributed to the atrio-ventricular (AV) node. The response to a vagal impulse is short-lived due to the activity on the SA and AV nodes having a short latency and from the quick response of the system to the release of the neurotransmitter, acetylcholine, which is broken down chemically by cholinesterase. This contrasts with the response to sympathetic

stimulation, which is more gradual since the adrenaline and noradrenaline released at the nerve endings are removed by the blood flow (Berne and Levy 1997).

The action of the vasoconstrictor system also has an effect on the heart rate since it influences the blood pressure which feeds back to the heart, increasing or decreasing the rate. There are a number of receptors in the system which detect these changes in blood pressure and relay the information to the autonomic nervous system; these are covered next (Guyton and Hall 1997).

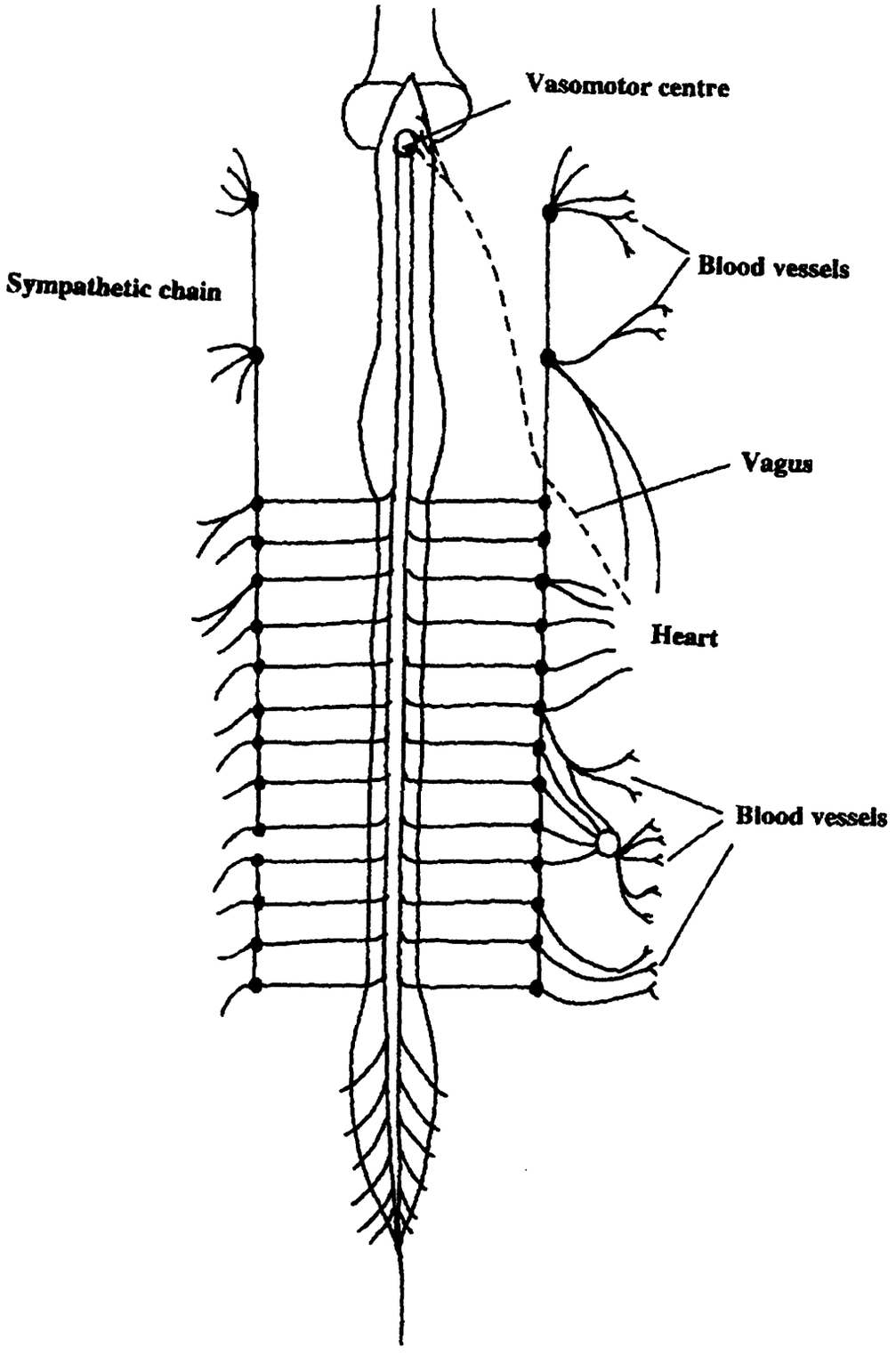


Figure 2.3: *Anatomy of sympathetic nervous control of the circulation (Guyton and Hall 1997)*

2.2.1 Baroreceptor reflex

The baroreceptors are a spray of non-encapsulated nerve endings and are found in the aortic arch and the carotid sinus; their function is to stabilise blood pressure. The baroreceptors respond to stretch rather than pressure and it is thought that the baroreceptors in the carotid sinus are more sensitive to change in pressure as the vessel walls here are much thinner. If, for example, an arterial distension coming from a rise in arterial pressure occurs, this will cause the baroreceptors to fire a burst of action potentials which, via a polysynaptic central pathway, decrease the heart rate by increasing the vagal and decreasing the sympathetic outputs to the heart and also causing vasodilation of veins and arterioles in the peripheral circulating system (Levick 1995, Guyton and Hall, 1997). For a low arterial pressure, impulses from the sympathetic system cause the heart rate to be high and for a high arterial pressure, low heart rate is produced by a vagal action from the parasympathetic nervous system. In the intermediate region the parasympathetic and sympathetic nervous systems act together in influencing the heart rate (Berne and Levy 1997).

The action of the baroreceptors is for short term control of large changes in arterial pressure rather than long term arterial pressure regulation (Levick 1995) and reduces arterial pressure variation by at least one half than that that would normally occur if they were not present (Guyton and Hall 1997).

2.2.2 Chemoreceptor reflex

The chemoreceptors are located in the bifurcation of each common carotid artery and in aortic bodies close to the aorta (Berne and Levy 1997). Their action is similar to that of the baroreceptors however the chemoreceptors respond to changes in blood gas concentrations: a lack of oxygen, excess of carbon dioxide or excess of hydrogen ions. The chemoreceptors are in close contact with the arterial blood supply; when the arterial blood pressure reduces to below a certain level, the amount of blood flowing reduces which increases the hydrogen ions and carbon dioxide and decreases the oxygen level in the blood. This change in the concentration of the blood gases stimulates the chemoreceptors and from the signals transmitted to the vasomotor centre, the arterial pressure is increased. This reflex is most active at low arterial

pressures (Guyton and Hall 1997) but often does not have a great effect in changing heart rate due to the two mechanisms at work. The primary effect of the carotid chemoreceptor is in decreasing heart rate through the medullary vagal centre; the secondary and over-riding effect from the arterial chemoreceptors arises due to respiratory stimulation and can inhibit medulla vagal centre action (Berne and Levy 1997).

2.2.3 Atria and pulmonary receptors

These are located in the atria and pulmonary arteries and have a similar function to the baroreceptors by minimising the change in arterial pressure following alterations in blood volume. These receptors act at low pressure and reinforce the action of the baroreceptors (Guyton and Hall 1997).

2.2.4 Ventricular receptor reflexes

The ventricular receptors are found near the endocardial surfaces of the ventricular walls. They have a similar function to the arterial baroreceptors and can be excited by a range of mechanical and chemical stimuli (Berne and Levy 1997).

2.2.5 Bainbridge reflex

It was found by Bainbridge in 1915 that fast infusions of blood or saline into anaesthetised animals caused the heart rate to rise, if it was initially at a low level. This also occurs in humans and here causes other responses such as the baroreceptor reflex which would act to reduce the heart rate due to the increase in arterial pressure (Ganong 2001). When the heart rate is initially high the action of the Bainbridge reflex causes the heart rate to slow (Berne and Levy 1997) and its overall effect is diminished (Ganong 2001).

2.2.6 Respiratory Sinus Arrhythmia

Variations in heart rate at the frequency of ventilation are present, namely an increase during inspiration and decrease during expiration, which correspond to increases in sympathetic activity and parasympathetic activity respectively.

A decrease in intrathoracic pressure as occurs during inspiration, implies that the venous return to the right hand side of the heart increases which activates the Bainbridge reflex to increase heart rate. Following a time delay, while this increased venous return reaches the opposite side of the heart, the arterial blood pressure will increase due to this raised left ventricular output which will stimulate the baroreceptor into reducing heart rate.

Variations in the peripheral resistance of arterioles at the respiration frequency caused by changes in sympathetic activity also give rhythmical fluctuations in arterial blood pressure which again invokes the baroreceptor reflex. The stretch receptors present in the lungs may also cause a change in heart rate as a reflex reaction to lung inflation. Movement of the rib cage arising from the respiratory centre in the medulla, also causes rhythmic changes in the heart rate at the respiratory frequency (Berne and Levy 1997).

2.3 Control of the stroke volume

Stroke volume also contributes to the cardiac output following each cycle of the heart. As will be seen, factors which cause stroke volume to change are not isolated and will also affect the heart rate; an outline of these factors is given here.

There are two main factors which act in opposition, the first comes from a change in arterial pressure. The second concerns the energy present in the cardiac muscle fibres which can be increased intrinsically by causing the cells to stretch during diastole, the application of the Frank-Starling law, or extrinsically from hormonal or chemical influences (Levick 1995).

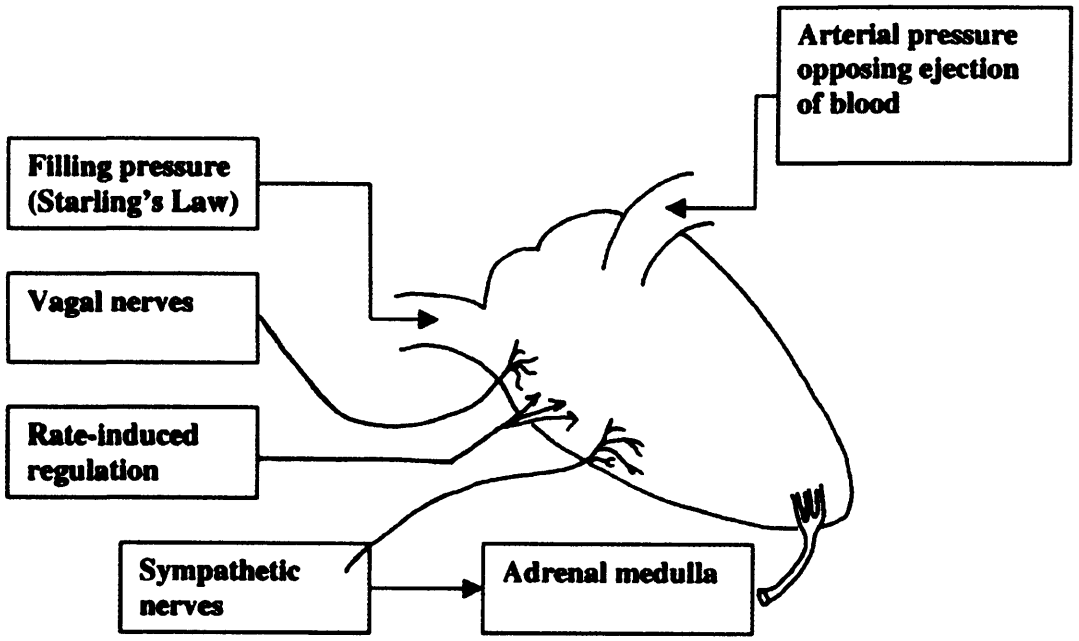


Figure 2.4: *Principal factors regulating stroke volume. (Adapted from Levick 1995)*

2.3.1 Intrinsic factor: Frank-Starling mechanism

This mechanism involves keeping an exact balance between the outputs of the left and right ventricles through a change in length of the myocardial fibres. This enables the cardiac output of the heart to be matched to the venous return through these compensatory actions.

Starling's work used an isolated canine heart-lung preparation; he found that when blood accumulates in the ventricles the myocardial fibres in the walls of the ventricles lengthen. This accumulation is due to a difference between ventricular inflow during diastole and ventricular outflow during systole arising from an increase in stroke volume and ventricular volume. This lengthening of the fibres causes an increase in stroke volume through ventricular contraction allowing equilibrium of venous return and cardiac output to be attained (Berne and Levy 1997).

2.3.2 Intrinsic Factor: Rate-induced regulation

The effects of rate-induced regulation depend on the rate of contraction of the muscle: for certain short intervals the force of the contraction will be much greater than that at longer intervals. This is caused by an increase in intracellular Ca++ content as the frequency of contractions is increased.

The changes in the length of intervals between the beats also causes a change in beat pattern since the first beat following this change will be feeble due to inadequate filling of the ventricle before the beat; the next beat though will be very strong due to the more exaggerated filling of the ventricle (Berne and Levy 1997).

2.3.3 Extrinsic factor: Nervous control

Extrinsic factors influence contractility, where an increase in energy occurs which is not due to a change in fibre length. Sympathetic influences are known to increase myocardial performance through enhancement of atrial and ventricular contractility. This arises from the release of noradrenaline which overall causes an increase in Ca^{++} levels thus increasing the heart's contractile strength.

The conduction system and atrial muscle are inhibited by the vagal nerves. Vagal influences can reduce ventricular contractility by overcoming sympathetic activity through the release of acetylcholine from nerve endings and thus reduce stroke volume, but it is thought that this has only a small effect in man (Levick 1995, Berne and Levy 1997).

2.3.4 Extrinsic factor: Chemical control

The adrenal medulla releases adrenaline and some noradrenaline into the blood stream; their rate of release is dictated by sympathetic activity, however under normal conditions their effect is small (Berne and Levy 1997). Angiotensin, also a hormone, acts on sympathetic nerve endings causing noradrenaline to be released (Levick 1995).

Calcium ions and some drugs including caffeine raise the concentration of free sarcoplasmic Ca^{++} ions and also increase contractility (Levick 1995). These extrinsic factors all contribute to an increase in stroke volume.

2.4 The electrocardiogram (ECG)

A resting muscle cell is classed as being polarised: inside the cell is negatively charged and outside is positively charged. When stimulated these charges change places making the cell depolarised. This happens in the heart: when the SA node (the heart's pacemaker) fires, the impulse spreads in this way throughout the atrial muscle and into the fibres connecting the SA node with the AV node. When the AV node fires it forces the action of the ventricles to pump the blood. By placing electrodes on the body, the potentials generated in the cardiac muscle during this depolarisation and repolarisation can be represented graphically as an ECG. This gives an accurate beat-to-beat measurement of the heart rate.

The ECG signal is shown below: the P-wave arises from atrial contraction, the QRS complex arises from the ventricular activation or depolarisation and the T wave represents ventricular recovery or repolarisation (Allen 1976, Tompkins 1993, Feleppa *et al.*, 1996 Martin 1998). In the case of the fetus during labour, an electrode is usually placed on a bony part of the skull and this allows the fetal heart rate to be monitored directly.

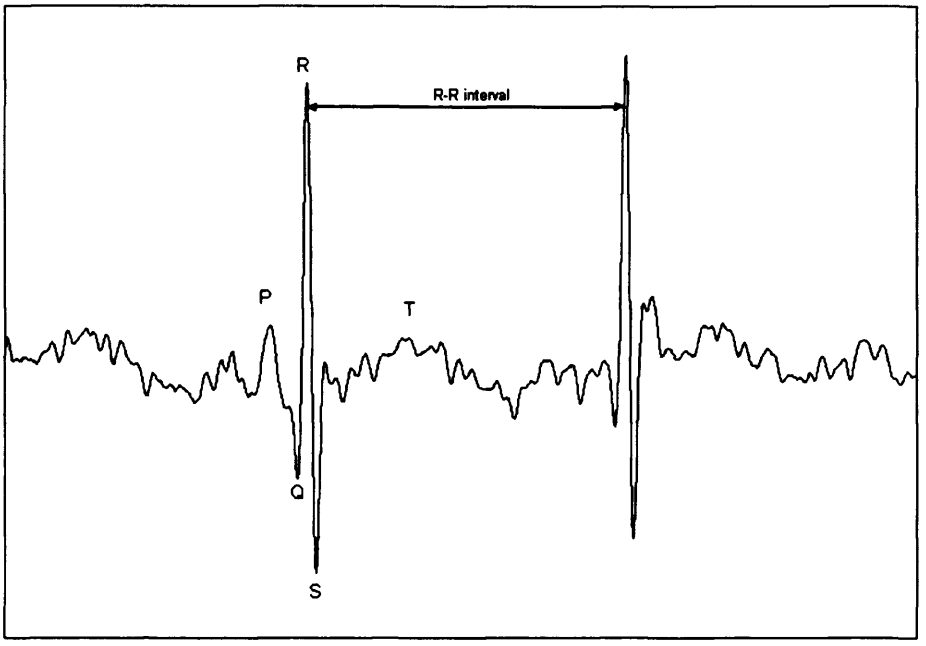


Figure 2.5: *The electrocardiogram showing the QRS complex and an RR interval.*

2.4.1 RR series

When the heart beats, the time taken for each cycle changes as the heart responds to conditions such as exercise or rest. The mean heart rate is mediated by the activity of the sympathetic and parasympathetic nervous pathways (Pieri *et al.* 2001). By detecting the time taken between successive R points in the ECG, the RR time series can be assessed and from this series, a measure of the heart rate variability can be obtained. When arrhythmia detection and elimination has been performed these intervals are termed normal-to-normal intervals (NN).

2.5 Heart rate variability and its uses

By analysing the RR series derived from the ECG, the variability in heart rate (HRV) can be found. This type of analysis has been used previously in many different areas but it is particularly useful in aiding assessment of autonomic function which

previously has only been possible using invasive methods. Two examples of the application of HRV analysis are: in assessing the prognosis following myocardial infarction and in looking at the damage to the autonomic nervous system caused in patients suffering from diabetes with neuropathy.

When myocardial infarction occurs, the blood flow to the cardiac muscle is obstructed, causing death to that segment of heart muscle. Following this, ventricular fibrillation may occur where the muscle fibres of the ventricles beat rapidly without pumping any blood to the heart (Martin 1998). Power spectrum analysis of HRV data measured over 24 hours has been shown to give reduced power in all frequencies in patients suffering from heart disease who have been resuscitated from ventricular fibrillation, in comparison to the spectra of normal subjects. It is thought that this type of analysis would be useful in providing early identification of patients at risk of sudden cardiac death, which other methods have had difficulty in categorising (Myers 1977). Another study has used this type of analysis to predict mortality in the 3 years following myocardial infarction (Bigger *et al.* 1992). Other work has used short and long-term recordings of HRV measurements to try to identify those patients at increased risk of mortality. Long term monitoring was found to be more strongly predictive of this (Fei *et al.* 1996).

A complication of diabetes mellitus is damage to the autonomic nerves, called autonomic neuropathy; the mortality rate associated with this condition can be as high as 50% in three years. The diagnosis of this condition is difficult due to the lack of quantitative tests and some patients do not always show the classic symptoms associated with this condition. It was thought that changes in heart rate would allow the presence of this damage to be detected. Assessing 24 hour HRV for those with neuropathy showed a reduction in HRV, in other diabetic patients without neuropathy, HRV was within the normal range but at the lower end (Malpas and Maling 1990). Power spectrum analysis of the R-R time series also illustrates the changes: a large decrease in the total power for the diabetic patients with neuropathy compared with normal patients, the LF peak could not be identified and the HF peak was greatly reduced. For the diabetic patients without neuropathy the LF/HF ratio showed the same type of behaviour as in normal subjects, however its reaction to changes, such as standing up was less obvious (Bianchi *et al.* 1990).

2.6 Concluding comments

The following two chapters will continue this discussion of heart rate variability by looking at time domain and frequency domain analysis of this signal in two different areas. There has been something of an explosion in the use of heart rate variability analysis applied to clinical problems which is probably due to the non-invasive nature of the collection of the data required for this type of investigation. It is this aspect which this study hopes to take advantage of when trying to detect fetal distress.

3.0 Fetal distress: A critical summary of the strengths and weaknesses of methods currently used for detecting fetal distress

3.1 Introduction

Fetal distress resulting from asphyxia prior to, or during labour, is caused by an insufficiency of uterine or umbilical blood flow, generally caused by a compression in the umbilical cord, or a decrease in maternal arterial oxygen content (Parer and Livingston 1990, Kean *et al.* 2000).

In all cases the amount of oxygen reaching the fetus is reduced, causing distress. This results in a decrease in pH of the fetal blood and a change in the beating pattern of the heart. The decrease in available oxygen, should it persist, can result in damage to the brain, cardiovascular complications or other organ damage producing problems such as cerebral palsy, mental retardation or hearing problems (Robertson *et al.* 1993, Low 1997). A study looking at school performance of those children who suffered mild, moderate or severe encephalopathy resulting from birth asphyxia found that those who suffered mild encephalopathy were free from neurological impairment. Those in the moderate and severe categories were at risk of physical and mental impairment and reduced school performance. Even those children in the moderate category who did not suffer notable impairments had a reduced performance at school in comparison with their peers (Robertson *et al.* 1989).

It has been found that in situations of fetal distress, if the decision to delivery time is 35 minutes instead of 15 minutes, the admission rate to the neonatal intensive care unit is doubled (Gibb and Arulkumaran 1997). In trying to prevent such situations, the occurrence of asphyxia prior to and during labour should be detected and reversed or if this is not possible then the baby should be delivered in the shortest possible time, to reduce the amount of damage and subsequent illness.

3.2 The fetal heart

The first sign of the embryo's heart appears at about day 18 of pregnancy, though the entire embryo is just under a millimetre in diameter. Much development occurs between this point and end of the third month, when the heart reaches its characteristic form. Further changes do occur between this point and birth but these are more of a preparation for the outside world rather than alterations in definition (Longmore 1971).

The parasympathetic control of the fetal heart is similar to that of the adult, however the sympathetic innervation is incomplete and this reduced number of sympathetic nerve fibres compared with the regular number of adrenergic receptors means that it is more sensitive to impulses. While in the womb, the two ventricles pump in parallel rather than sequentially as in postnatal life (Gillan 1995). Karin *et al.* (1993) have found through spectral analyses of fetal heart rate data at antepartum, from young pregnancies (gestational age 23 weeks) and mature fetuses (gestational age 40 weeks) that the younger fetuses had a higher level of heart rate variability due to their less organised neural activity in comparison with mature fetuses.

The main methods available for detection of fetal distress during labour look at two of the symptoms of distress already noted, the pH of the fetus' blood and the change in the fetal heart rate. In the next section these methods of intrapartum monitoring will be looked at noting the advantages and problems associated with their use; antepartum monitoring will be touched on in the final section.

3.3 Intrapartum monitoring: Fetal blood sampling

The idea of fetal blood sampling was introduced by Saling to allow an indication of hypoxia to be found (Llewellyn-Jones 1982). If there is reason to believe that the fetus may be suffering distress, then the pH is checked by taking a sample of blood from the baby's scalp.

The pH, noted to be the only test which can give a definitive diagnosis of fetal asphyxia (Low 1999) is still considered by some to be the 'best widely available technique' for detecting asphyxia during labour (Nelson and Emery 1993). It is easy to see why: the analysis of the sample of blood, once taken, can be performed relatively quickly giving a pH level which is then compared to a threshold producing an unequivocal response regarding the presence of acidosis. The 8th Annual CESDI Report attest to the specificity of fetal blood sampling as an indicator of fetal well-being.

There are some drawbacks in using this method, the most important being that the measure is not continuous. If the measure is taken during a normal deceleration in heart rate, in a healthy fetus, an incorrect diagnosis of hypoxemia may be found. It is also possible for the status of the fetus to change, invalidating the pH reading soon after it has been taken. Therefore to be able to detect distress and prevent injury occurring, pH samples would have to be taken at intervals short enough that damage following distress would not have had time to occur. The procedure of taking a sample of blood from the baby's scalp during labour is invasive and can cause some distress and discomfort to the mother, so unnecessary repeated readings are not advised. Where a problem has arisen which is detected by a decreased pH level, there is little information available about the nature of the insult (Low 1997).

Kubli *et al.* (1969) noted that in the presence of an 'innocuous fetal heart rate pattern' the pH did not alter. Apart from in severe cases, the amount of change in pH and amplitude drop in fetal heart rate did not correlate with variable decelerations of heart rate, but as will be seen in the next section, the analysis of electronic fetal heart rate records in diagnosing distress is not always definitive.

3.4 Intrapartum monitoring: Heart rate monitoring

During labour the fetal heart rate may be monitored by intermittent auscultation using a stethoscope or by electronic methods where a printed trace showing the average heart rate along with an instantaneous numerical measure of the average heart rate is produced.

3.4.1 Intermittent auscultation

This technique has been used since the early part of the nineteenth century with Hohl's introduction of the fetal stethoscope (Gibb and Arulkumaran 1997); measurements are performed for 1 minute every 15 minutes between contractions. There are certain disadvantages to this method, such as subjectivity, the inability to detect small changes in rate and the lack of objective information about variability (Smith 1995).

3.4.2 Intermittent auscultation compared with electronic heart rate monitoring

Haverkamp *et al.* (1976) studied 483 high-risk patients comparing both these methods of monitoring and found no improvement in perinatal outcome following electronic monitoring and suggested that the one to one nursing care available to these patients monitored using auscultation was important in achieving a positive outcome. In practice however, one to one care may not always be possible. Similarly Nelson *et al.* (1996) note that "more than 20 years and 11 randomised trials later, electronic fetal monitoring appears to have little documented benefit over intermittent auscultation with respect to morbidity or long term neurological outcome" and the American College of Obstetrics and Gynaecology have concluded that electronic fetal heart rate monitoring and intermittent auscultation collected at specified intervals are equivalent: they do not promote the use of one method over another (Carter *et al.* 1993).

However Menticoglou and Harman (1999) have studied four cases in low-risk pregnancies where, had intermittent auscultation been used alone, the asphyxia which occurred in each case would not have been identified: detection was through the decreased variability, the baseline heart rate was completely normal.

3.4.3 Electronic fetal heart rate monitoring (EFHRM)

The standard piece of equipment used for this type of monitoring is the cardiotocograph (CTG) and there are various types in use made by different manufacturers. The CTG produces a printed record of mean fetal heart rate and

contractions against time. The mean fetal heart rate and uterine activity are also expressed numerically.

The fetal heart rate is found from one of two ways, either by attaching an ultrasound transducer to the mother's belly or by using a fetal electrode clipped to the baby's scalp. In most cases the signal from the ultrasound transducer is sufficient for displaying the fetal heart rate however in certain circumstances such as difficulty in achieving a good signal or if it is suspected that the fetus is distressed, the scalp electrode may be used. This technique is invasive and therefore is only used when deemed necessary. The tocograph signal for the contractions is collected using a second transducer, attached to the mother's belly.

Reasons for monitoring in this way include maternal illness such as diabetes or hypertension, obstetric complications for example a previous caesarean section or other risk factors including tobacco use (Sweha *et al.* 1999). When used, this method of monitoring is relied on heavily for providing information about fetal well being through identification of heart rate patterns and should a problem occur which is later investigated, the printed records can be referred to as evidence.

Considering the widespread use of EFHRM, this should imply the reliability and sensitivity of this equipment in detecting fetal distress; this is not the case. Following its introduction in the 1960s (Parer and King 2000), it was thought that fetal injury and death due to distress occurring during labour would disappear, but this has not happened. The improvements in fetal outcome have only been slight which may be due to an increase in caesarean section rate, another consequence resulting from the use of EFHRM.

EFHRM achieves a greater amount of detail about the heart rate than the previously used intermittent auscultation (Neilson 1993). The continuous nature of the data collection and printed record of the fetal heart rate are also seen as advantages (Neilson 1993). It has been suggested (Sweha *et al.* 1999) that when used properly, EFHRM may be superior to fetal blood sampling in predicting a good or poor outcome and Berkus *et al.* (1999) remark that EFHRM can identify some patients who

are at a greater risk of abnormal outcome; Low (1999) notes some decrease in the number of intrapartum deaths with fetal monitoring.

The discussion regarding the interpretation of fetal heart rate patterns which started following the introduction of EFHRM is still going on today. Carter *et al.* (1993) report that the 'hoped for benefit has not been realised,' Sweha *et al.* (1999), regard fetal heart rate monitors to be unproven technology and Murphy *et al.* (1990) suggest using more fetal blood sampling until better methods of fetal monitoring are found, but as shown above, this brings its own difficulties.

The main question comes in deciding which patterns definitely highlight a problem and which do not (Paul and Hon 1974, Paul *et al.* 1975, NICHD 1997, Huddleston 1999); there is a tendency for fetal heart rate monitors to produce false positive results (Low 1999, Sweha *et al.* 1999). This is not the fault of the equipment, but rather a problem in interpretation (Huddleston 1999). The CESDI study for Wessex (1995) reported a 'failure to recognise abnormal CTG recording' in 21% of cases from 1993 to 1995, which was comparable to results found throughout Britain in 1994; other studies have also shown low levels of consistency between observers for CTG traces (Lotering *et al.* 1982, Parer and King 2000, Zimmer *et al.* 1998). Parer and King (2000), in their US based study reason that this is due to a lack of standardised nomenclature and management guidelines for fetal heart rate pattern interpretation and the CESDI for Wessex (1999) recommend that a guideline on the use of EFHRM should be available in every delivery unit.

3.4.4 Using fetal heart rate variability to detect distress

There has been a considerable amount of work in looking at fetal heart rate variability to ascertain whether this can be used to provide an indicator for fetal distress. One of the most important points about these studies, is to note the definition of fetal heart rate variability being used. In particular, the clinical definition of heart rate variability in this context, which is the amount of variation around the baseline rate, is different to that being used here. Some authors use 'short-term' and 'long-term variability' others prefer to talk about variations around baseline heart rate. Examples of such studies include: Samueloff *et al.* (1994) who compared five scoring systems suggested

by other researchers, which looked at the height of FHR amplitude variation or frequency of oscillations for their measure of fetal heart rate variability; conclusive results showing fetal distress were not found. Parer *et al.* (1985) also compared the work of others in finding indices for short and long-term variability: short-term variability was quantified by a number of different indices but long-term variability proved to be more difficult.

The use of indices in quantifying the variability in heart rate data present in a record mark the start of work towards an entirely computerised method of analysing traces.

3.4.5 Automated detection of fetal distress

Automated systems for analysis of intrapartum heart rate data which have already been proposed include Taylor *et al.* (2000) who tested an algorithm in real-time which showed good results for baseline fetal heart rate and number of decelerations but little agreement with experts in other situations. Dawes *et al.* (1991) implemented a computerised analysis of heart rate data and defined long-term variability as the mean range of pulse intervals per minute and short-term variability as the mean epoch to epoch variation over intervals of 3.75s. They found that changes which cause fetal heart rate variability to decrease are not always associated with fetal hypoxemia.

The use of power spectral analysis of heart rate variability data for the detection of distress has also been studied. Min *et al* (2002) looked at this during acute hypoxia in fetal lambs and found significant increases in low frequency power and the ratio of low frequency to high frequency power in relation to the baseline level and concluded that this method could be a more quantitative, objective and sensitive method of distress detection. Westgate *et al.* (1999) also looked at the response of fetal lambs to cord occlusion through the analysis of short-term variation (the average of the R-R intervals over 3.75 seconds) and MMR, the difference between maximum and minimum R-R intervals every minute. They did not find any uniform pattern of changes in fetal heart rate variation which related to the length of occlusion, rather that the heart rate response to cord occlusion is complex. Oppenheimer and Lewinsky *et al.* (1994) found that an increase in low frequency power occurred during a

contraction and decreased following the end of the contraction in the normal fetus, but this change did not occur in fetuses with severe acidosis at delivery.

ST-segment analysis of the ECG is another automated method, which uses the ratio of the amplitude of the T-wave to the amplitude of the R-wave and that when this is plotted it can show up problems occurring during labour. Westgate *et al.* (1992) conducted a study into this and found there was potential for the use of this method; Amer-Wåhlin *et al.* (2001) compared this method with standard cardiotocograph monitoring and found an improvement in the ability of obstetricians to identify fetal hypoxia. A further ST trial comparing STAN (ST-segment analysis equipment) and CTG in Plymouth, the first randomised controlled trial undertaken, backed up these findings and established some of the benefits of STAN including the better understanding of the physiology producing the ST waveform change, the reduction in intervention compared with sole use of the CTG and the ability to use a different measure from data which is already collected (Rosen and Luzietti 1994). Machines which perform this analysis are now available for use in clinical practice.

3.5 Antepartum monitoring

Fetal heart rate monitoring also plays a part in monitoring the health of the fetus prior to labour. Injury may take place at any time: Low (2003) reports in a recent study, that of 1182 pregnancies delivered preterm, 70 fetuses were found to have suffered asphyxia. Of these fetuses, 30 were delivered before the onset of labour and about half of these fetuses suffered moderate or severe asphyxia; the same was true for the intrapartum group. Those fetuses delivered through an early intervention or Caesarean section were found to have suffered higher levels of asphyxia. This is an interesting problem particularly for very young fetuses, when it is suspected that they may be suffering from a problem, whether to deliver immediately or allow the fetus to stay in the womb until later in its gestation: the factors affecting premature deliveries against further hypoxic damage must be balanced. Of particular importance is the monitoring of those fetuses who are growth retarded: it may be difficult to ascertain whether that fetus is suffering from the condition of intrauterine growth retardation or is constitutionally small.

The Growth Restriction Intervention Trial (GRIT) study (1996) recognised the uncertainty between obstetricians in the case of whether to deliver high-risk growth retarded fetuses and found that collective uncertainty exists where even if an obstetrician is sure that their course of action is best, other obstetricians do not necessarily agree.

Specifically looking at fetal heart rate monitoring, the same inconsistencies and disagreements exist in interpreting heart rate patterns at antepartum as at intrapartum. Pardey *et al.* (2002) describe a computer system for automated analysis of the fetal heart rate records, the Sonicaid system, which has been under development since 1978. It imitates the analysis an observer would undertake and produces an advisory report for the clinician to act on. This system is available commercially and has been introduced into some maternity departments.

3.6 Conclusions

For intrapartum monitoring, fetal blood sampling is invasive and sometimes difficult to perform, but does give an easily interpretable result, however this is not a continuous method of monitoring. Intermittent auscultation, also a discontinuous but staff intensive method of monitoring, was an early non-invasive method of providing information about the heart rate but its use in some circumstances has been questioned. Electronic fetal heart rate monitoring, which is now widely used at antepartum and intrapartum suffers from problems in interpretation of traces. It has been noted that this difficulty with analysis arises due to there being too much information available about the fetal heart rate. The usefulness of automatic detection of fetal distress has been hinted at. There is a need within the busy clinical environment of the delivery suite to be able to connect a patient to a monitor and within a reasonable time interval be able to read overall results without the need for lengthy interpretation. So far, these ideals have not been met; some methods have given new approaches to an old problem, with that of the ST-segment analysis being the most successful for intrapartum monitoring following its implementation in some obstetric departments but this is only applicable for those patients being monitored

invasively. At antepartum the Sonicaid system for computerised heart rate pattern interpretation is being used but the time required for assessment of well-being can be lengthy particularly in cases where a problem may exist. For maximum effectiveness, a method of collecting data which is continuous and non-invasive and that can be processed within a short timescale, allowing a definite interpretation to be made, would be useful.

4.0 A study on the optimum order of autoregressive models for heart rate variability

4.1 Introduction

When performing signal analysis it is often useful to consider the component frequencies which make up the signal; this is the case when looking at a string of consecutive RR intervals representing heart rate variability. Power spectral analysis of RR intervals identifies up to three frequency components that can be associated with identifiable physiological mechanisms: the very low frequency band (VLF), occurring between 0 and 0.03Hz caused by thermoregulation and humoral factors; the low frequency component (LF), centred around 0.1Hz which comes from baroreflex-related heart rate variability; and the high frequency component (HF), occurring between 0.18 and 0.4Hz, which arises from the respiratory sinus arrhythmia (RSA) (van Ravenswaaij-Arts *et al.* 1993, Cerutti *et al* 1995). The high frequency component reflects modulation of vagal tone whereas the lower frequency components are influenced by both parasympathetic and sympathetic systems. As Malik and Camm (1993) point out, it should be emphasised that this is the modulation of autonomic tone and not the action of the autonomic tone since this would imply that each vagal impulse fired by the autonomic nervous system was represented, which of course occurs at a much higher frequency than 0.4Hz.

Both parametric and non-parametric methods are used for frequency domain analysis and examples of both will be summarized below. These methods have trade-offs associated with them and so the selection of an appropriate method for the data being analysed is important.

4.2 Fourier based spectrum analysis

Spectrum analysis is often performed using a Fourier-based technique simply because this is the first-line engineering approach to spectrum analysis and because FFT

functions are so widely available. Two examples of classical methods of spectrum analysis include the Blackman-Tukey method and the periodogram. The Blackman-Tukey method uses estimates of autocorrelation lags from the original data, windows these and then uses the Fourier transform to obtain the power spectrum density function. The periodogram approach performs a fast Fourier transform on the data set and squares these output values.

Both of these methods assume the signal being analysed is periodic and in using Fourier transforms express the signal as the sum of sine and cosine functions. Windowing the data causes leakage in the frequency spectrum: the convolution of the desired transform with the transform of the window function can spread the true power of a signal into adjacent frequency bins. This convolution also implies that the width of the main lobe of the response of the signal is limited by that of the window, which limits the frequency resolution of the signal to the inverse of the time period (Kay and Marple 1981).

4.3 Parametric power spectrum analysis

Autoregressive (AR), moving average (MA) and autoregressive-moving average (ARMA) models can be used in performing power spectrum analysis. These methods differ from the previously described Fourier based methods in that the signal being analysed is assumed to be the output of a mathematical model. This model provides the relationship between the input, a white noise driving source and the output. The power spectrum is then found from the parameters used in fitting the signal to the model (Cerutti *et al.* 1995). Using a model in this way gives a better frequency resolution, particularly for short segments. The signal is assumed to continue behaving in a similar way and the mean and standard deviation remain the same.

The autoregressive model, which will be discussed here, results in linear equations and thus has an advantage over moving average (MA) and autoregressive moving average (ARMA) models (Kay and Marple 1981).

4.3.1 The autoregressive model

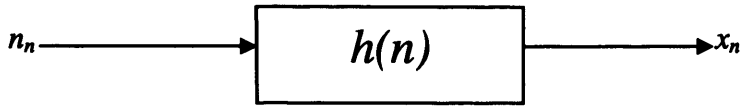


Figure 4.1: *Diagram showing an autoregressive process with a white noise driving source input n(n), impulse response h(n) and output x(n).*

The output of the autoregressive process shown above can be written as:

$$x_n = -\sum_{k=1}^{p} a_k x_{n-k} + n_n \qquad (4.1)$$

where a_k are the parameters of the model.

H(z), the system function between the input and output is the z-transform of h(n) and can also be written as:

$$H(z) = \frac{1}{A(z)}$$

where

$$A(z) = \text{z-transform of AR branch} = \sum_{m=0}^{p} a_m z^{-m}$$

The relationship between the power spectrum of the output of the linear filter and the power spectrum of the input to it is

$$P_x(z) = H(z)H^*(1/z^*)P_n(z) = \frac{P_n(z)}{A(z)A^*(1/z^*)}$$

and evaluating this along the unit circle $z = \exp(j2\pi f\Delta t)$ for $-1/(2\Delta t) \le f \le 1/(2\Delta t)$ with an input white noise driving source of zero mean and variance σ^2 leads to

$$P_{AR}(f) = \frac{\sigma^2 \Delta t}{|A(f)|^2}$$

where $A(f) = A(\exp[j2\pi f \Delta t])$, which can be expressed as

$$P_{AR}(f) = \frac{\sigma^2 \Delta t}{\left|1 + \sum_{k=1}^{p} a_k \exp(-j2\pi f k \Delta t)\right|^2}$$

To allow this power spectrum to be found, the AR model parameters must be computed.

The two most popular methods available for finding the AR parameters are Burg's method of maximum entropy estimation and the Yule-Walker equations (Kay and Marple 1981).

Here, a description of the linear relationship between the autocorrelation function and the AR parameters using the Yule Walker equations is given.

4.3.2 Autocorrelation function

This is used to estimate the parameters required for the model by providing a way of describing the signal whose power spectrum is being calculated. This works by looking at the parameters of the actual signal and then shifting the signal in time and multiplying the actual signal by the lagged one which overall gives the autocorrelation function. The values in the centre are more reliable than those at the tails since more values have been used in calculating these; they are also the more recent values which may have a greater effect on the outcome of the current value (Lynn and Fuerst 1997). The autocorrelation function is written as

$$R_{xx}(k) = E[x_{n+k} x_n^*] = E\left[x_n^*\left(-\sum_{l=1}^{p} a_l x_{n-l+k} + n_{n+k}\right)\right]$$

$$= -\sum_{l=1}^{p} a_l R_{xx}(k-l) + E\left[n_{n+k} x_n^*\right]$$

which reduces to

$$R_{xx}(k) = \begin{cases} -\sum_{l=1}^{p} a_l R_{xx}(k-l) & \text{for k>0} \\ -\sum_{l=1}^{p} a_l R_{xx}(-l) + \sigma^2 & \text{for k=0} \end{cases}$$

These are the Yule-Walker equations and the AR parameters can be found by solving for p equations and also σ^2. Expressing this in matrix form using the equations k=1,2.....p which result from the part of the autocorrelation function with the fewest lags and including σ^2:

$$\begin{bmatrix} R_{xx}(0) R_{xx}(-1) ... R_{xx}(-p) \\ R_{xx}(1) R_{xx}(0) ..... R_{xx}(-(p-1)) \\ \text{M} \\ R_{xx}(p) R_{xx}(p-1) . R_{xx}(0) \end{bmatrix} \begin{bmatrix} 1 \\ a_1 \\ \text{M} \\ a_p \end{bmatrix} = \begin{bmatrix} \sigma^2 \\ 0 \\ \text{M} \\ 0 \end{bmatrix}$$

The Levinson-Durbin algorithm is a recursive algorithm used to solve these equations. This calculates the parameters $\{a_{11}, \sigma_1^2\}, \{a_{21}, a_{22}, \sigma_2^2\}$ up to $\{a_{p1}, a_{p2}, ... a_{pp}, \sigma_p^2\}$ at order p, which are the AR parameters for that model order. The time of computation for this algorithm is $t \propto p^2$ and if using the matrix, $t \propto p^3$.

The algorithm is initialised using

$$a_{11} = -R_{xx}(1) / R_{xx}(0)$$
$$\sigma_1^2 = (1 - |a_{11}|^2) R_{xx}(0)$$

and for k=2,3....p

$$a_{kk} = -\left[R_{xx}(k) + \sum_{l=1}^{k-1} a_{k-1,l} R_{xx}(k-l)\right] \Big/ \sigma_{k-1}^2$$

$$a_{ki} = a_{k-1,i} + a_{kk} a^*_{k-1,k-i}$$

$$\sigma_k^2 = \left(1 - |a_{kk}|^2\right)\sigma_{k-1}^2$$

The autocorrelation function is essential here, the only problem is caused by the tradeoff between using the correct level of complexity to provide the best imitation of the signal being analysed against a workable length of computation time. The rest of this chapter looks at the selection of the 'correct' model order, where 'correct' is that model order which satisfactorily meets this trade-off.

4.3.3 Using AR spectral analysis for HRV signals

The advantages associated with using autoregressive modelling for power spectral analysis have already been mentioned: of particular interest in this work is the property of improved spectral resolution for short frames of data (Marple, 1977). An inconvenience however, of AR-based spectral analysis is that the order for the AR model which best represents the series must be estimated prior to the spectral analysis. Criteria for the estimation of the model order to be used have been published, however, as noted by Kaluzynski (1989) and by Schlindwein and Evans (1990), these tend to underestimate the order when applied to AR spectral estimation of Doppler blood flow signals.

The work presented in this chapter is concerned with finding adequate AR model orders for spectral analysis of short segments of the time series formed from RR intervals. Jones (1974) noted that Akaike's final prediction error (FPE) and Akaike's information criterion (AIC) tend to predict identical model orders for the same frames of measured data. This will be investigated for HRV data and also compared with the results from Parzen's criterion of autoregressive transfer-function (CAT) and Rissanen's minimum description length method (RIS). The resulting spectrum using the overall recommended order will be compared with spectra obtained using different AR model orders (both above and below the estimated 'optimum') and to the

spectrum obtained using the non-parametric (Fourier-based) approach to estimate the effect that choosing the wrong order has on the AR spectrum.

4.4 Data acquisition and pre-processing

The data was obtained from two sources: the first was a 24-hour Holter recording of a normal 19-year-old adult (subject 1) using a Mortara recorder; secondly, 6 files from the MIT-BIH arrhythmia database (MIT-BIH, 1992) were used: 5 of these files with mainly normal complexes (subjects MIT-100, 101, 112, 113 and 122) and 1 file with some pre-ventricular complexes (MIT-233). For subject 1 the QRS complexes were detected and a series of successive R-R intervals were produced and recorded as a raw tachogram. Since ectopic beats are independent from the control mechanisms that modulate the heart rate, a simple algorithm was implemented for rejection of ectopic beats and arrhythmic events which is performed as such: if(RR(k)>0.7*(RR(k-1)+RR(k+1))), then RR(k)=(RR(k-1)+RR(k+1))/2. For the 6 records of MIT-BIH data, the annotated detection marks have been used as fiducial points for the detection and the arrhythmia rejection part of the algorithm has not implemented. This was done to see how much the presence of arrhythmias in subject MIT-233 influenced the estimated AR orders. The raw tachogram consists of samples of data whose time intervals are not uniform, but instead refer to consecutive R-R events, that is, it is a time-event series. A cubic spline interpolation was used for re-sampling the series at a constant rate of 4 Hz, to give equal sampling intervals in time and to allow traditional spectral estimation with frequency measured in Hz rather than mean heart rate. The data was then sectioned into non-overlapping frames of $N = 128$ samples, each frame was de-trended and analysed individually.

4.4.1 Model order estimation

Four criteria were used for the estimation of the optimum model order. The first was Akaike's Final Prediction Error (FPE) criterion (Akaike, 1969), described as

$$FPE_p = \sigma_p^2\left(\frac{N+p+1}{N-p-1}\right)$$

where N is the number of data samples and σ_p^2 is the estimate of the prediction error power for model order p.

The second technique used for estimating the model order was Akaike's information criterion (AIC) (Akaike, 1974):

$$AIC_p = \ln(\sigma_p^2) + \frac{2(p+1)}{N}$$

The third criterion was Parzen's criterion autoregressive transfer function (CAT) (Parzen, 1975):

$$CAT_p = \left(\frac{1}{N}\sum_{j=1}^{p}\frac{N-j}{N\sigma_j^2}\right) - \frac{1}{\sigma_p^2}$$

where σ_j^2 is the intermediate prediction error power for j = 1 to j= p.

The final technique was Rissanen's minimum description length method (RIS) (Rissanen, 1984)

$$RIS_p = \sigma_p^2\left(1+\left(\frac{p+1}{N}\right)\ln(N)\right)$$

For all four techniques, mean square error and bias change for each model order used and the above-defined functions have a minimum point; the model order corresponding to this minimum point is said to be the optimum.

4.5 Estimating the optimum order for the given data

Each set of data was tested using the four criteria described above and histograms of the optimum model order for each set of data were produced. The data and histograms from subject 1 (normal) are shown in figure 4.1. It can be seen that overall the model

order chosen most frequently for the data over the 24 hours was $p = 5$ for FPE, AIC and CAT, but for RIS it was $p = 2$ and with a narrower spread in the histogram.

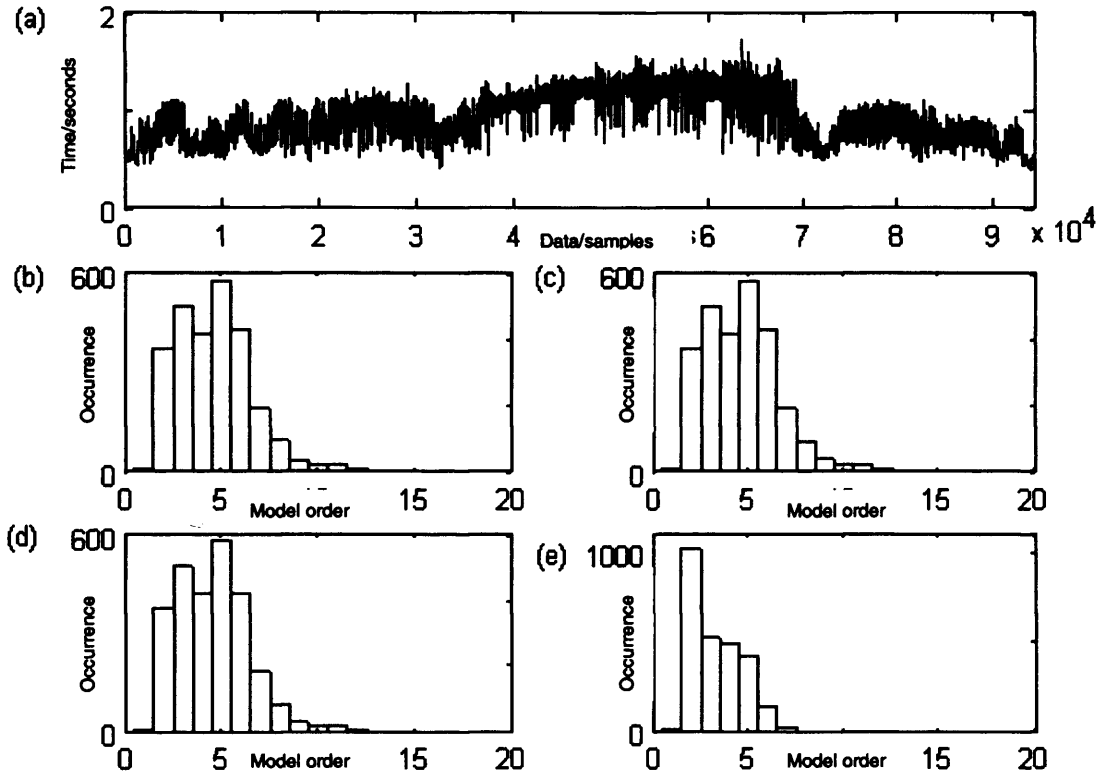


Figure 4.1 - *(a) Plot of the tachogram signal from subject 1 in data samples, where each point corresponds to an RR interval. The histograms show the optimum model order (x-axis) as found by the (b) FPE, (c) AIC, (d) CAT and (e) RIS criteria corresponding to the tachogram shown in (a).*

For the MIT-BIH subjects the estimated order ranged mostly up to p=6, and in no case was higher than p=16, as illustrated in figure 4.2 for subject MIT-100. This was similarly true for the other 4 subjects with mostly 'normal' beats. For the record of subject MIT-233, which contains some pre-ventricular cycles, the range of model orders estimated was wider, up to p=22. The corresponding histogram is shown in figure 4.3.

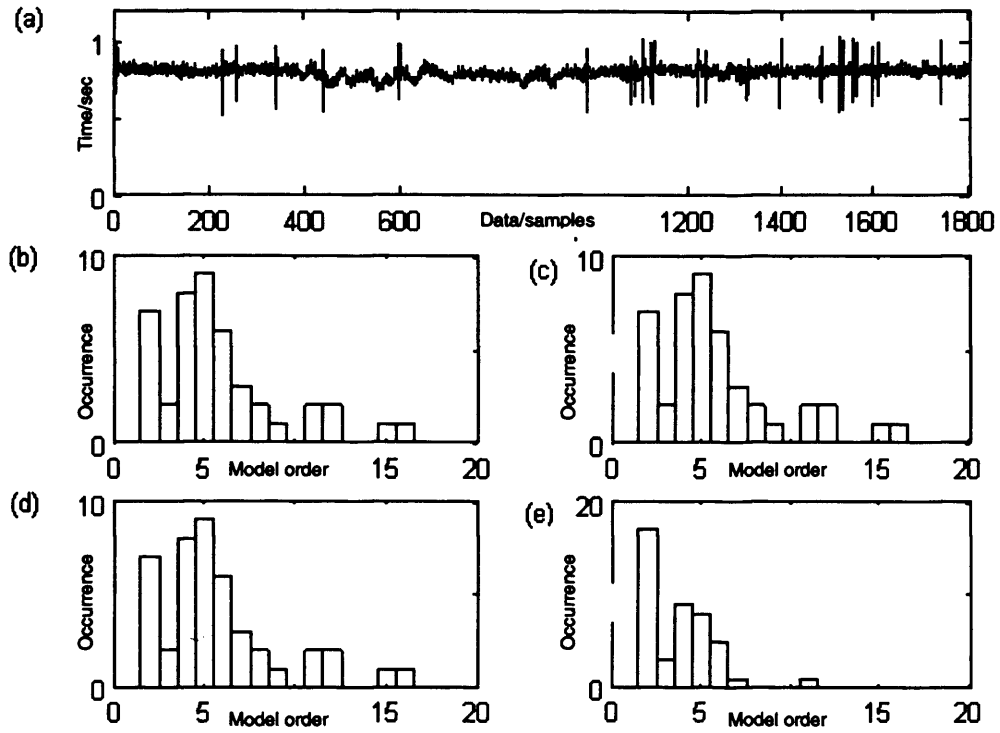


Figure 4.2 – *Plot of the tachogram signal (a) from subject MIT-100, in data samples, where each point corresponds to an RR interval. The histograms showing the optimum model order (x-axis) as found by the (b) FPE, (c) AIC, (d) CAT and (e) RIS criteria corresponding to the tachogram shown in (a).*

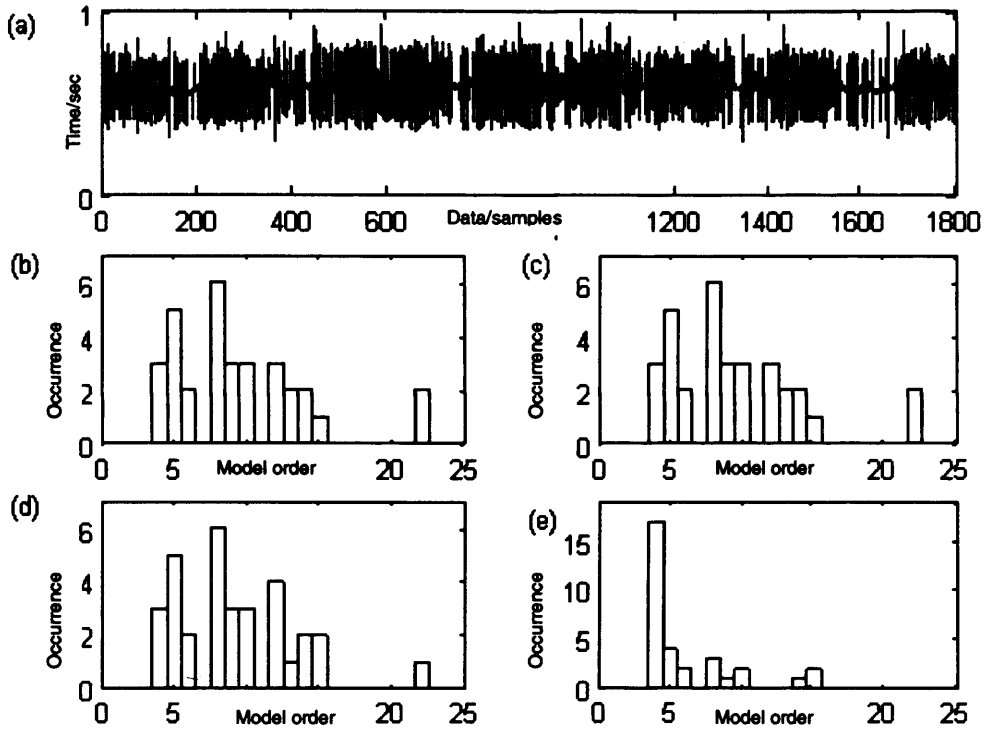


Figure 4.3 – *Plot of the tachogram signal (a) from subject MIT-233, in data samples, where each point corresponds to an RR interval. The histograms show the optimum model order (x-axis) as found by the (b) FPE, (c) AIC, (d) CAT and (e) RIS criteria corresponding to the tachogram shown in (a). The ECG of this subject included some ectopic beats (mostly pre-ventricular cycles) and these were left untouched and included in the processing.*

It has been found here that all four techniques frequently produce an underestimation of the required AR model order for spectral analysis. It was stated in the introduction that, in general, it would be expected that three frequency components might occur, corresponding to very low, low and high frequency, each associated with different physiological mechanisms. This situation would require a model order of at least p = 6 to correctly estimate the AR based power spectrum. It must be noted here that due to the very short length of the data frames used, it is not possible to estimate the VLF component. Although the AR spectral analysis technique fares better than FFT-based approaches for short segments, since each of the segments is 32 s long, it is expected that only frequencies above 0.031 Hz will be estimated correctly.

The underestimation of the correct AR order and its effect on the spectra is illustrated by figure 4.4(a) where the AR-based power spectra for 500 frames of night-time data for subject 1 have been obtained using an order $p = 5$. If this is compared with the power spectra obtained for the same data using an order $p = 16$, shown in figure 4.4(b), it is found that the RSA peaks in the spectrum are more easily identified for the higher order model. These spectra can also be compared with the corresponding Fourier-based (modified periodogram) spectra shown in figure 4.5. Note that, due to the fact that short frames of 32 s are used, the resolution of the FFT-based spectrum suffers, and the evidence of this is that the peaks at RSA are quite weak.

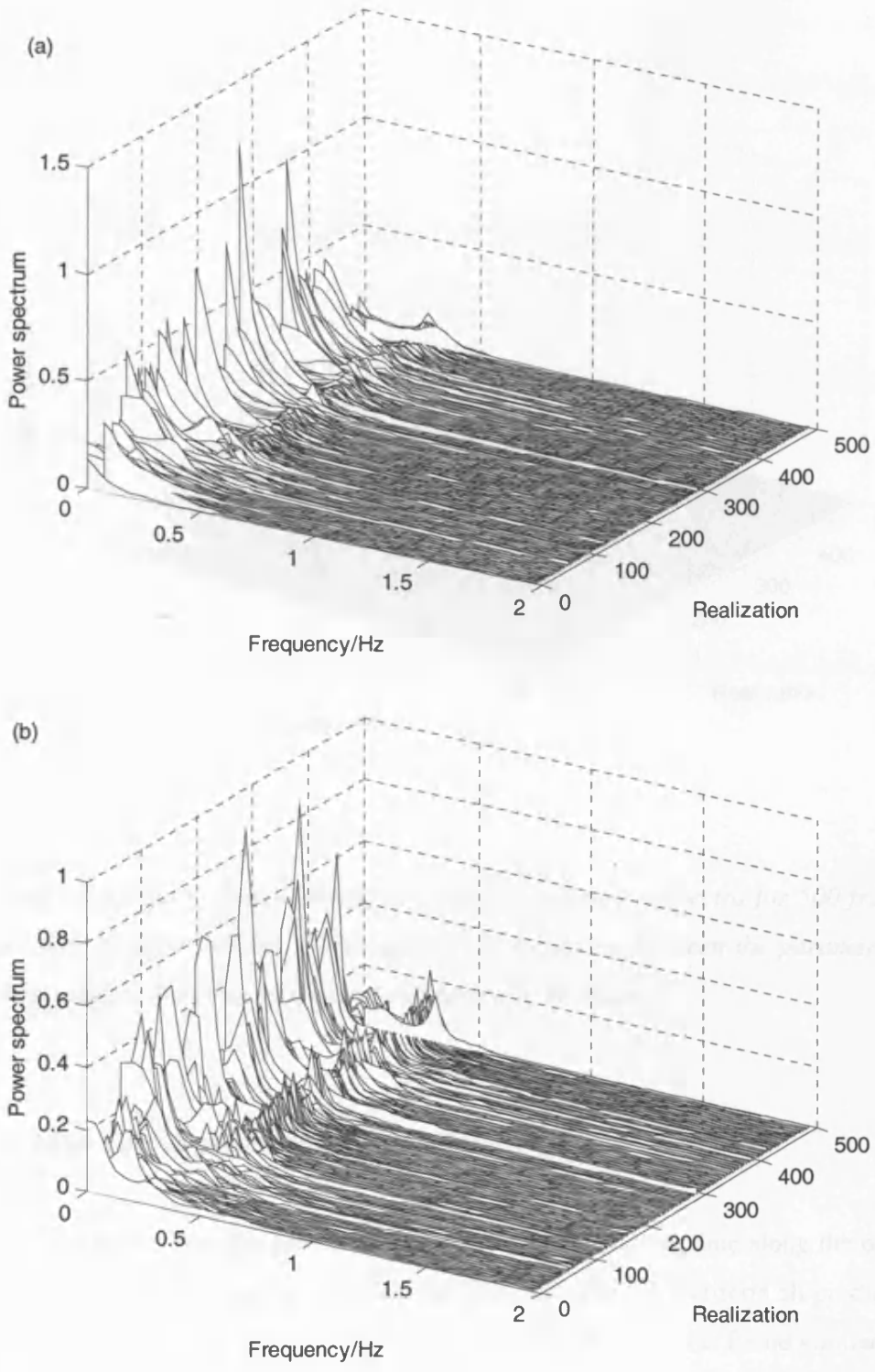


Figure 4.4 - *AR power spectra for 500 frames of night-time data for subject 1 using the recommended AR order of p=5 (a) and p=16 (b). It can be seen that the increased model order improves spectral resolution.*

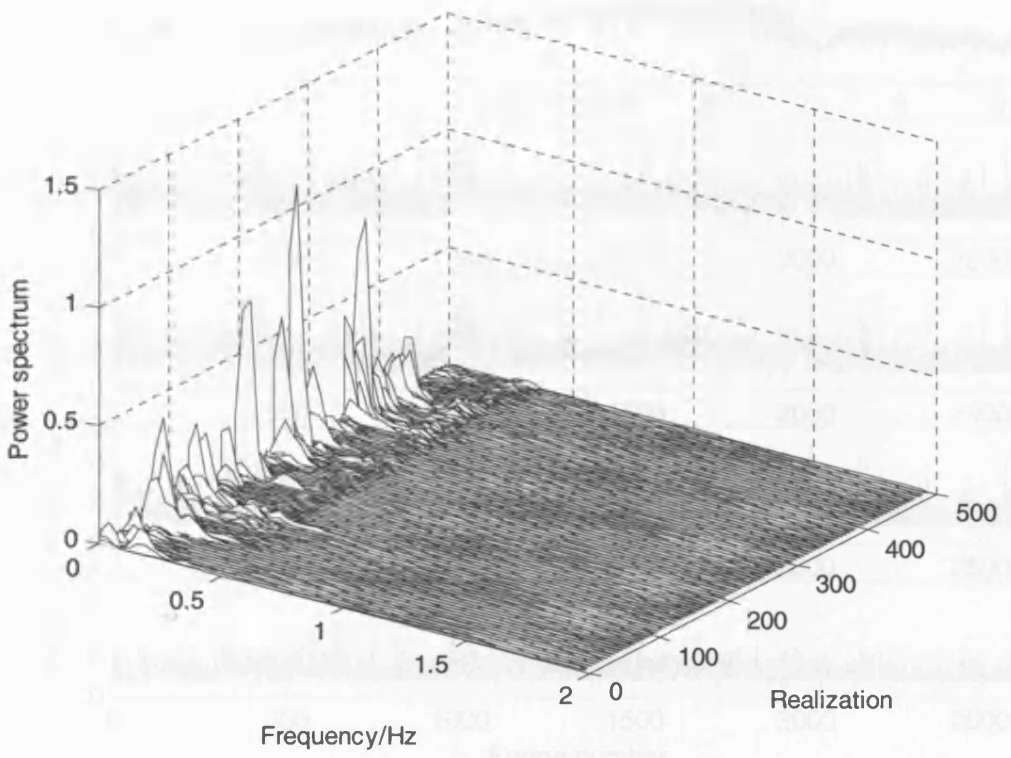


Figure 4.5 - *Fourier-based (modified periodogram) power spectra for 500 frames of night-time data for subject 1. This allows a comparison between the parametric and non-parametric methods of spectral estimation to be made.*

4.5.1 Model order progression

Figure 4.6 shows how the predicted model order changed over time along the original signal for subject 1. It can be seen that the FPE, AIC and CAT criteria all predict practically the same model order for each frame of data. This was found similarly for the other sets of data. The behaviour of the orders predicted using AIC and FPE agrees with the conclusions of Jones (1974), who stated that these two criteria normally predict identical model orders for the same frames of data. Rissanen's criterion, however, often estimates a lower model order compared to the other three criteria, as seen in figure 4.6(e).

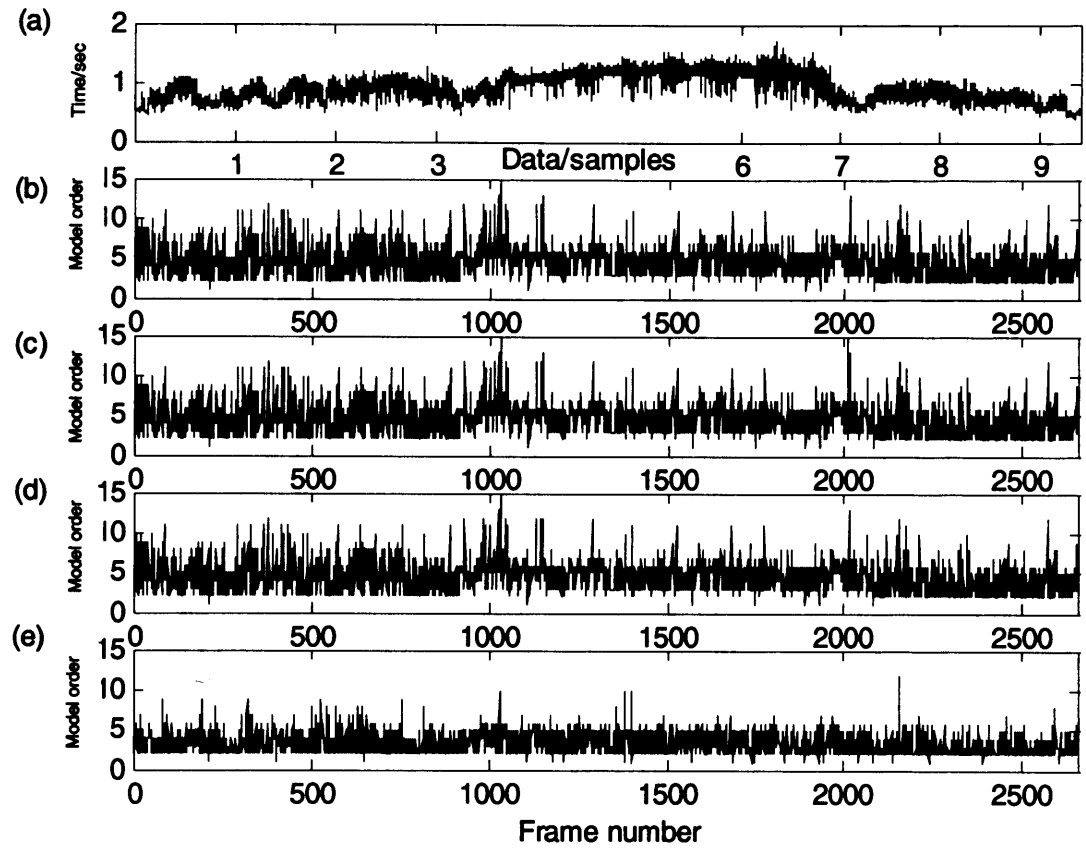


Figure 4.6 - *Plot of the signal (a) for subject 1 for 24 hours and the progression of the AR model order as predicted by (b)FPE, (c)AIC, (d)CAT and (e)RIS. It can be seen that nearly all the predicted model orders are the same for the first three criteria, but RIS estimates smaller orders.*

4.5.2 Sampling frequency

The model orders estimated by the above four prediction criteria for an autoregressive process cannot be discussed without considering the re-sampling frequency used in conjunction with the cubic spline interpolation. From Nyquist, this should be at least twice the highest expected frequency component present in the spectrum (the fastest possible change in heart rate is the situation where there is a short interval followed by a long one repeated, implying that the fastest frequency is half the mean heart rate), but not so high that the signal is over-sampled.

In this part of the work all of the data was analysed using re-sampling frequencies of 2, 4 and 8Hz and the orders estimated using the FPE criterion (AIC and CAT also estimate similar orders) are given in figure 4.7 for subject 1. It can be seen that for a re-sampling frequency of 2Hz the model orders estimated range roughly from 2 to 10, with a peak at p=4; for a re-sampling frequency of 4Hz this distribution shifts slightly to the right, meaning that higher orders are needed, as expected; but for a frequency of 8Hz this shift occurs in the opposite direction: this wasn't expected and no explanation for this has been found.

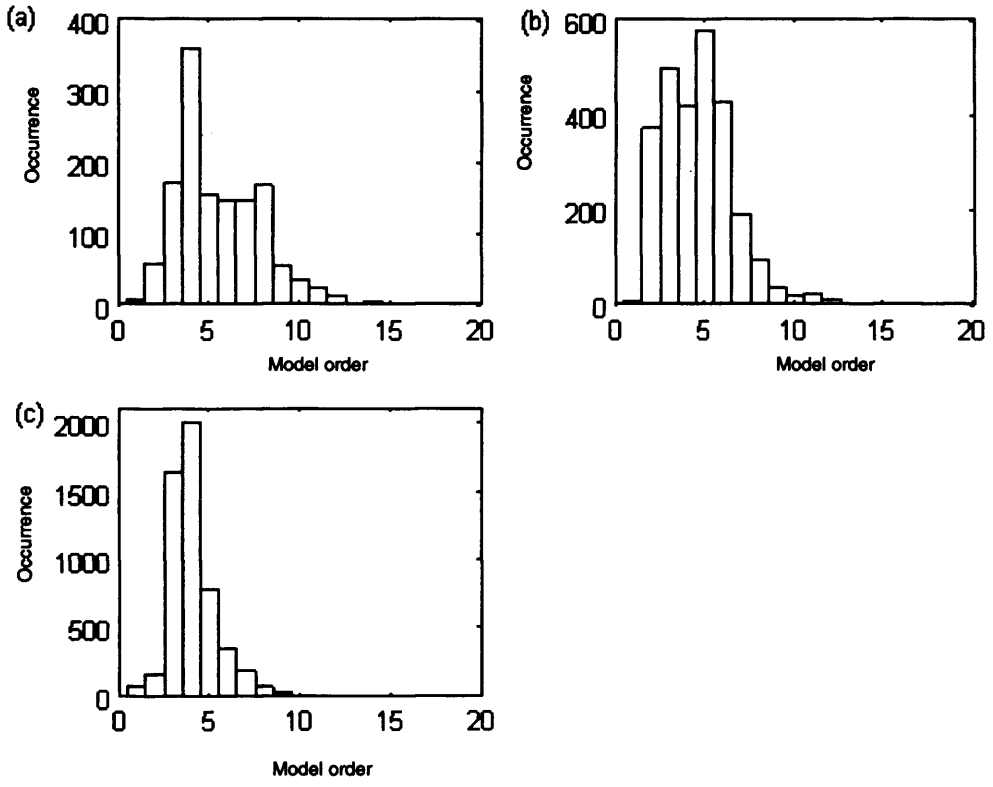


Figure 4.7: *Model orders estimated using FPE for re-sampling frequencies of (a) 2Hz, (b) 4Hz and (c) 8Hz. It was expected that the estimated AR model orders would increase with the re-sampling frequency and this happens for the transition from 2 Hz to 4 Hz, but not for the 8 Hz re-sampling frequency.*

4.6 Testing the order prediction criteria using a true AR process

The next part of this work allowed the four model order prediction criteria to be tested using a Monte-Carlo simulation of a *true* AR process. This was done by creating a true AR signal with a known order, $p = 6$, using coefficients extracted from the actual signal (to preserve its characteristics) and the filter given by equation 4.1. To allow the system to stabilise, each realisation of this test signal was produced from the last 128 of 1024 filtered values; this was repeated to produce 1000 realisations. The filter coefficients were found from one of the frames of the actual data used in the first part of the work for an order 6 system. Order 3 was predicted most often but, since in the general case it is intended to identify up to 3 frequency components, an order of at least $p = 6$ would be required. As said before, due to the very short segments used the VLF component cannot be accurately identified, but since LF and HF are relatively close, an AR order larger than 4 (twice the number of frequencies) is needed to estimate the AR-based spectrum.

Histograms were plotted showing the results obtained and these can be seen in figure 4.8. It was again noticed that the four model order prediction criteria more often than not underestimate the correct model order. Increasing the frame length to include N = 1024 samples resulted in a peak in the most frequently predicted AR model order at $p = 4$, and with a wider distribution to the right, i.e., higher orders got selected more often than when N=128. The histograms of the distributions for N=1024 can be seen in figure 4.9.

4.7 Specifying a fixed model order

From the results discussed so far it is apparent that for power spectrum analysis of all normal HRV data over short segments, the four prediction criteria do not consistently predict model orders which could be used to find accurate power spectra for the associated data. For short segments (N=128) of known AR processes,

underestimations of the correct order are produced more often than not, as shown in figure 4.8. It can therefore be concluded that none of the four criteria is suitable for application to short segments of HRV data. Even with many samples (N=1024) of true AR processes the orders predicted vary considerably and often the estimated order was smaller than the true order, as summarised in figure 4.9.

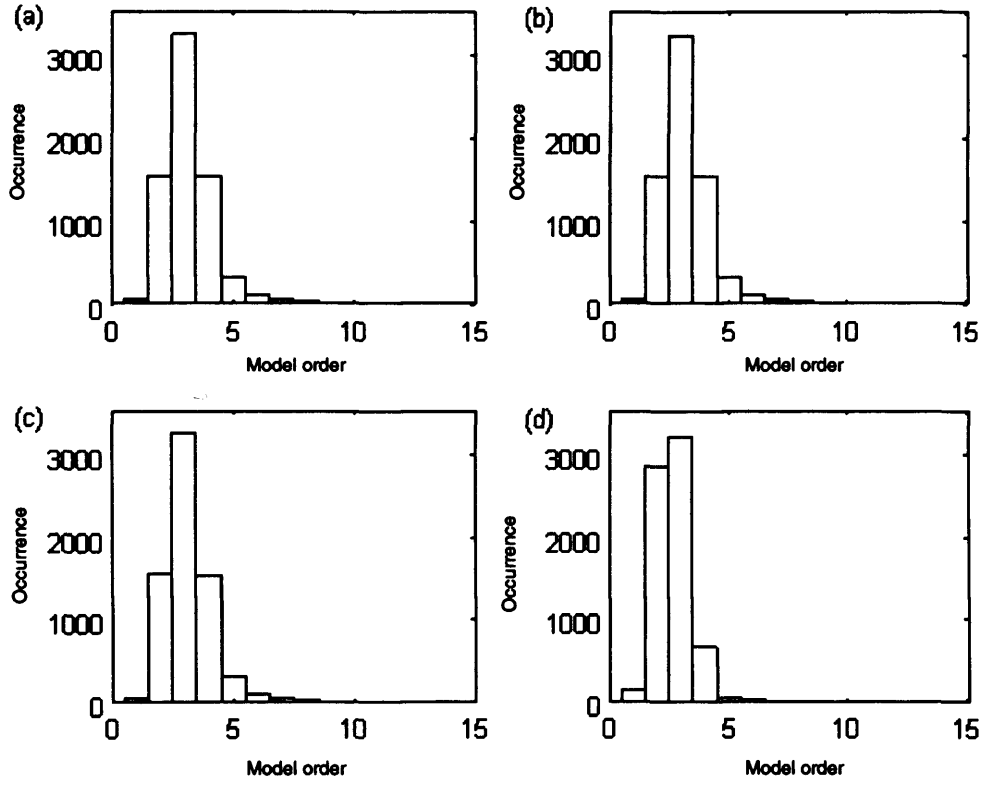


Figure 4.8 - *Histograms showing the 'best' orders predicted by (a) FPE, (b) AIC, (c) CAT and (d) RIS, resulting from the analysis of realisations of a true AR signal of order 6, each realisation containing N=128 samples. The histograms show that the order is underestimated by all 4 criteria.*

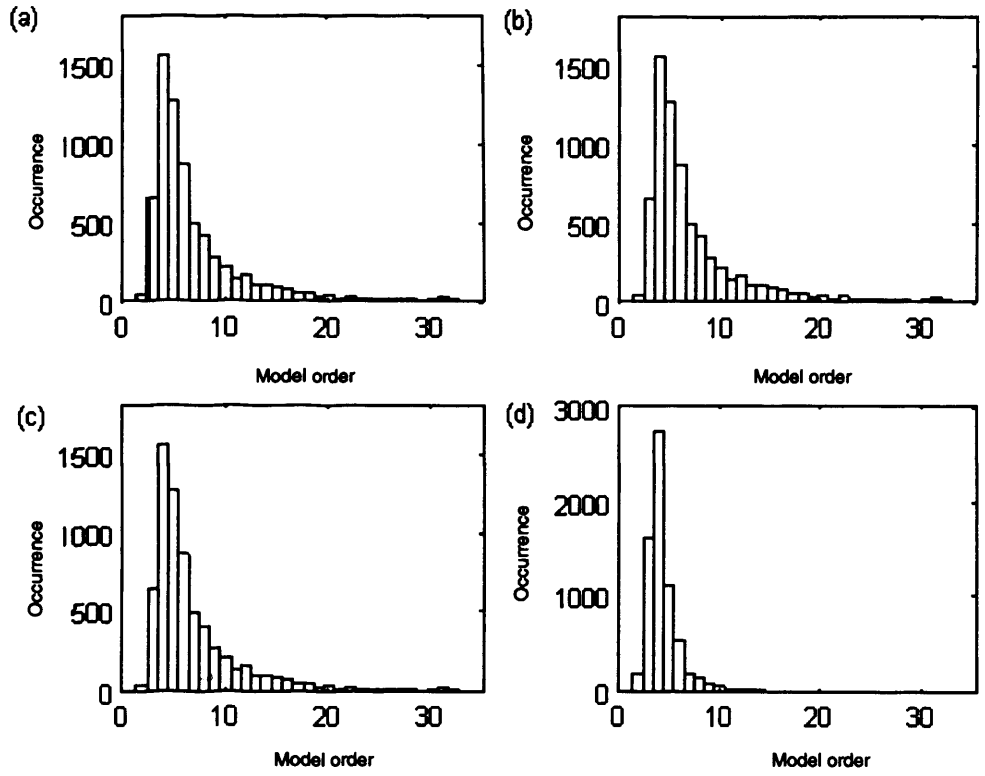


Figure 4.9 - *Histograms showing the 'best' orders predicted by (a) FPE, (b) AIC, (c) CAT and (d) RIS resulting from the analysis of realizations of a true AR signal of order p=6, each realization containing N=1024 samples. It can be seen that order 4 is predicted most by all 4 criteria, but higher orders are predicted more often than for the case where N=128, with RIS tapering sooner than the other 3 methods.*

It is proposed then, that a fixed model order should be used, the advantage being that it resolves the problem of varying predicted orders while still allowing 'good' spectra to be produced. A survey was conducted using 7 frames of data from each subject and producing power spectra for each frame for orders increasing in multiples of 2, from p= 10 to p=32. One set of these results is shown in figure 4.10 along with the relevant pole-zero diagrams.

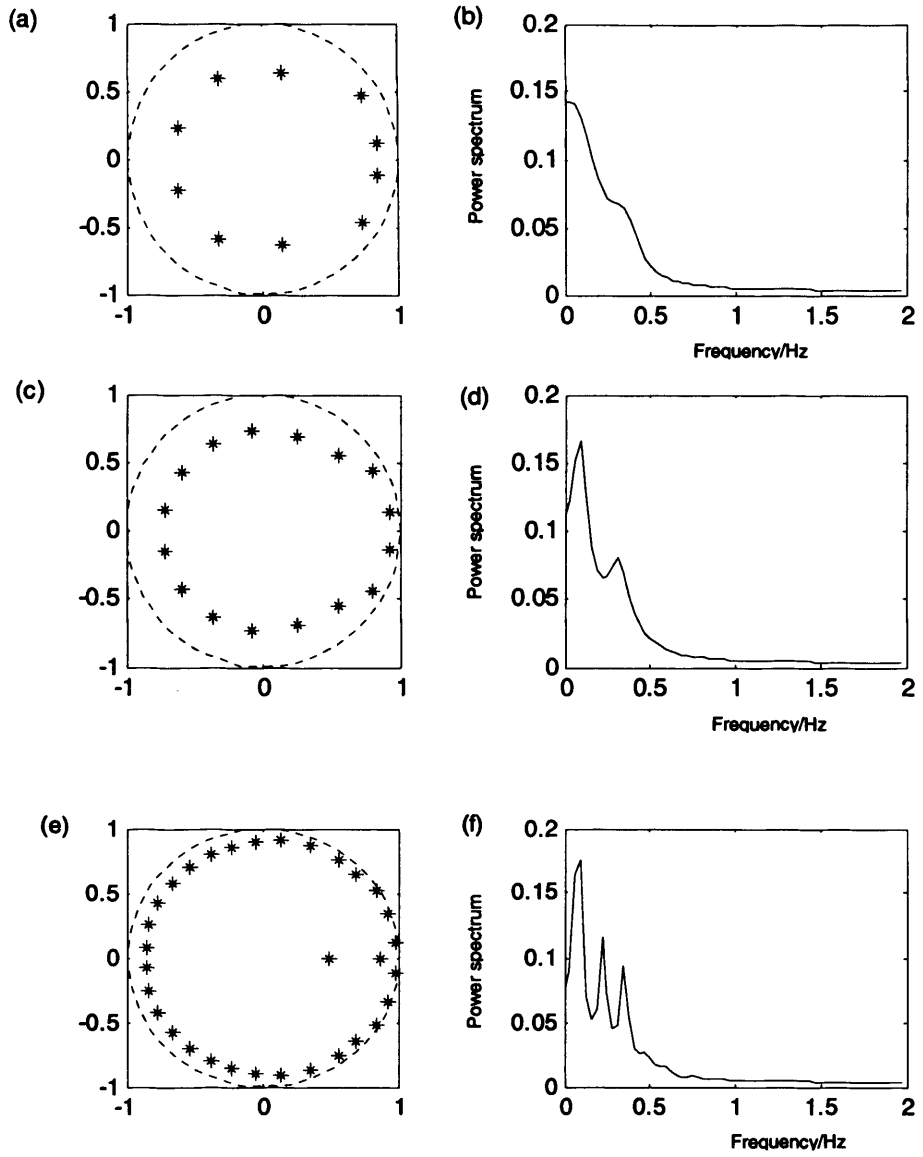


Figure 4.10 - *This comparison shows the effect that changing the model order has on the spectra for one specific frame of data. In (a) and (b) the AR model order is p = 10; in (c) and (d) the model order is p = 16, and for (e) and (f) the model order is p = 32. It can be seen that for p=16, the spectrum shows definite spectral peaks without spectral smearing or peak splitting.*

The pole-zero diagram is a very compact way of displaying the properties of a system and provides an alternative way of visualising its frequency response. When the poles appear equally close to the edge of the unit circle, it implies that they have roughly equal influence on the spectrum. For a pole away from the unit circle, closer to its centre, the implication is that this pole, or its corresponding filter coefficient, does not contribute significantly to the overall spectrum.

It was found that the lowest model order required to accurately show all spectral components for the different frames behaved in the following way: in the worst case, for p=10 to p=14 the spectra were damped and smeared; for p>22 spurious peaks occurred frequently. Between p=16 and p=22 there was no noticeable change in the spectra and it is desirable to use the lowest order possible since this parsimony reduces computation time. In all cases, for a model order of p=16, the spectra contained easily resolvable peaks and no spurious peaks or smearing. For these reasons p=16 is recommended as the optimum fixed model order to be used in this type of analysis.

4.8 Conclusions

Overall it has been found that 3 of the 4 criteria (FPE, AIC and CAT) estimate similar values for each set of data tested. However this value is very often an underestimation of the true AR model order when short segments (N=128) are used, and this gives rise to damped power spectra whose true separate frequency components cannot be recognised.

It was found that for longer frames of data (N=1024) FPE, AIC and CAT criteria all gave an improved estimate for the optimum model order when a simulated AR signal of known order was tested.

It was confirmed that underestimating the AR model order has more dramatic effects on the spectral estimation than overestimation, with only gross overestimation producing spurious spectral peaks.

The re-sampling frequency used for the spline interpolation was found to influence the predicted model order and over-sampling the signal would simply result in longer processing time being required, but with no benefits for AR spectral estimation.

To allow an accurate estimation of the power spectrum of RR time series signals re-sampled at 4 Hz, the order obtained from using the prediction criteria should be raised slightly, or alternatively (and this approach is preferred) an overall fixed order around $p = 16$ should be used.

5.0 Detection of asphyxia using heart rate variability

5.1 Introduction

5.1.1 Time domain analysis of HRV

The ability to identify frequency components in a signal and in particular a series of RR intervals has been demonstrated in the last section. However it is not only the frequency components which show variability in the signal, by looking at analysis in the time domain, different information about the characteristics of the heart beating period can be found, which may ultimately be used in diagnosis.

This isn't to say that time domain analysis shows a completely new set of results, as Bigger *et al.* (1992) point out, correlation between quantitative parameters in the time and frequency domains is high. However methods of qualitative analysis such as plotting histograms of beat periods can prove to be useful in spotting anomalous data points, sometimes disguised in other methods of analysis. The use of the Poincaré plot, a scatter diagram of present beat interval against previous beat interval, can give useful visual information which can be plotted in real-time (Kamen *et al.* 1996) and some knowledge of autonomic activity can be gained (Pitzalis *et al.* 1996). This also has the advantage of not requiring ectopic or arrhythmic events to be eliminated from the data recording thus giving a fuller picture of the activity occurring (Kamen and Tonkin 1995). Extra information, may also be found from this type of plot: Schectman *et al.* (1992) in their study of heart rate dynamics of infants who succumbed to sudden infant death syndrome (SIDS) compared with matched control infants, used a modified version of the Poincaré plot and found a change in heart rate in one direction was more likely to be followed by a change in the opposite direction in SIDS victims. Kamen and Tonkin (1995) through their work in assessing functional status in heart failure, speculate that Poincaré plots could be used to look at nonlinear mechanisms or other complex interactions that control the action of the heart, not dealt with in traditional time and frequency domain analysis.

5.2 Background to this work

The work covered in this chapter uses data obtained from adult rats asphyxiated for different lengths of time obtained at the John Hopkins University Baltimore. This study tests the feasibility of using measures of HRV i) to detect asphyxia when it is occurring and compare the accuracy of response of this measure to pH data; ii) following the insult, to detect that asphyxia has occurred and to estimate the severity comparing these results with a neurological assessment. The analysis of these data is performed in the time and frequency domains: in the time domain different time scales can also be used to allow patterns to be identified. Short-term analysis is used for identifying quick changes in heart rate and long-term analysis is concerned with slower fluctuations occurring in a longer time window (van Ravenswaaij *et al.* 1993).

ECG data was collected continuously, the pH of the blood was measured at regular time intervals and neurological status of the rats was also recorded in the form of a neuroscore. It is expected that during asphyxia a decrease in pH will occur since a function of the blood is to supply oxygen to the tissues and remove the products of metabolism, which include carbon dioxide. A neurological scoring system has been used as an objective measure of the neurological status and condition of the rat which can be monitored after the asphyxic episode. It is well known that disruption to the oxygen supply for a length of time causes damage to the brain and central nervous system and this has been observed in a number of studies, particularly those concerning birth asphyxia. It is thought that 'central' autonomic changes are caused by brainstem injury therefore the use of HRV will help to assess injury in critical brainstem areas.

5.3 Methods

5.3.1 Data Collection

In this work, 24 Wistar adult rats weighing 300-350 g were anaesthetised, intubated, had their femoral artery cannulated, and each rat was then submitted to a single period

of transient asphyxia for 0, 1, 3, 5, or 7 minutes; two of the rats were used as controls (sham experiments) and underwent the same surgical experimental procedure but without any period of asphyxia, hence the 0 minutes above.

The rats were anaesthetised using 3% halothane; at the onset of unconsciousness the trachea was intubated and connected to a ventilator delivering 50:50% nitrogen: oxygen and 0.5-1.5% halothane. Before the insult, 100% O_2 was used to wash out the halothane and nitrous oxide for three minutes and this was followed by room air for two minutes. The asphyxia was then induced by stopping ventilation and clamping the tracheal tube for 1, 3, 5 or 7 minutes. Resuscitation using 100% O_2 with administration of adrenaline at 0.01 mg/kg intravenously followed for the animals submitted to 3-7 minutes of asphyxia. The control rats and those subjected to 1 minute of asphyxia had spontaneous recovery and did not require resuscitation.

The data collected included continuous ECG and EEG data (collected at 333 Hz using a 12-bit A/D converter), blood gas data, and neurological scoring for up to 72 hours after the experiment; the rats were then sacrificed for pathological examination of the nervous tissues. The neuroscore used here is a modified version of the neuro-deficit score suggested by Katz *et al.*, (1995), and takes into account consciousness, brainstem function, motor assessment, sensory assessment, coordination, respiration and seizures. It has a scale of 0-80 where a normal rat scores 80 and a dead rat 0. Details of the results using the EEG and definition of the neuroscore were published elsewhere (Geocadin *et al.* 2000).

5.3.2 Signal processing

A classical 'derivative filter' followed by comparison with an adaptive threshold technique was employed for QRS detection. For the 'derivative filter' a second order Butterworth band pass digital filter with cut-off frequencies of 5 Hz and 36 Hz was chosen. The adaptive threshold was heuristically adjusted and tended to 65% of the running average of the peak of the magnitude of the QRS complexes.

It was not possible to use recordings that were free from ectopic beats and noise, so an absolute refractory period of 112 ms was used to reduce the possibility of detecting

'false positives' This value was chosen heuristically following experiments. The test for arrhythmic beats which eliminated most of the ectopic beats replacing them with the interpolation of the preceding and successive beat is performed using: if(rr(k)>0.7*(rr(k-1)+rr(k+1))), then rr(k)=(rr(k-1)+rr(k+1))/2. The new RR sequence after this test and interpolation is referred to as the NN series.

The segmentation of the signal was done using 30 s long frames and in each, an array of the time distance between consecutive fiducial points of the QRS was saved, along with their standard deviation. The NN signal was then resampled at 8 Hz after cubic spline interpolation for the analysis. This means that Nyquist criterion would be respected for signals with heart rate up to 480 bpm. Our experiments showed this to be adequate except in a few cases where, following administration of adrenaline in the resuscitation procedure, the heart rate might rise up to 500 bpm during a couple of minutes.

5.3.3 Analysis

In performing analysis of the data, two approaches were used: one to highlight that asphyxia was occurring (which can be used for detection) and another to show that asphyxia had occurred and to estimate how serious the injury was. These included using measures of HRV in both the time and the frequency domains and in the short-term and long-term.

In showing that asphyxia was occurring, a short-term measure of HRV using 30s averages of the standard deviation of NN intervals and 30 second averages of heart rate were plotted against time; in the frequency domain Fourier modified periodogram and autoregressive (AR) analysis with model order $p = 20$ were used to estimate the HRV spectra. (The choice of the AR model order was through tests using the model order predication criteria detailed in chapter 4). The blood gas concentrations, plotted against time were also used.

The second approach, to show that asphyxia had occurred and estimate its severity, used, in the very short-term, Poincaré phase plots (NN_i *vs.* NN_{i-1}) and in the long-

term, histograms of the NN intervals to show the variation over longer segments (5-20 minutes) of the signal.

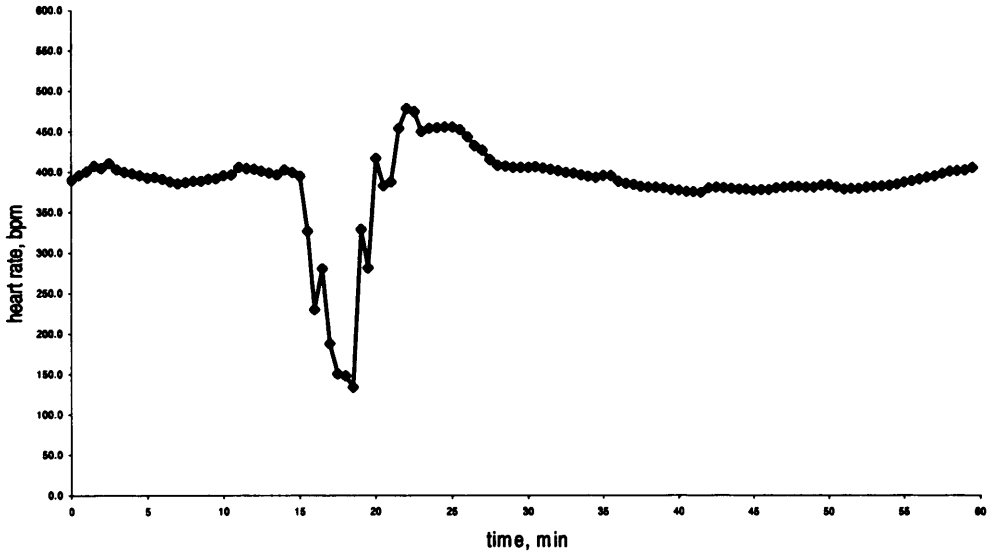
Neuroscores provided an alternative (from the ECG data and its analysis) estimation of the severity of the neurological damage caused by the episode of asphyxia.

Student's *t*-test was used to determine the significance of changes in HRV during and neuroscore and pH immediately after asphyxia normalised with the baseline level, compared to the control experiments; values of $p \leq 0.05$ were classed as significant.

5.4 Results

5.4.1 During asphyxia

(a)



(b)

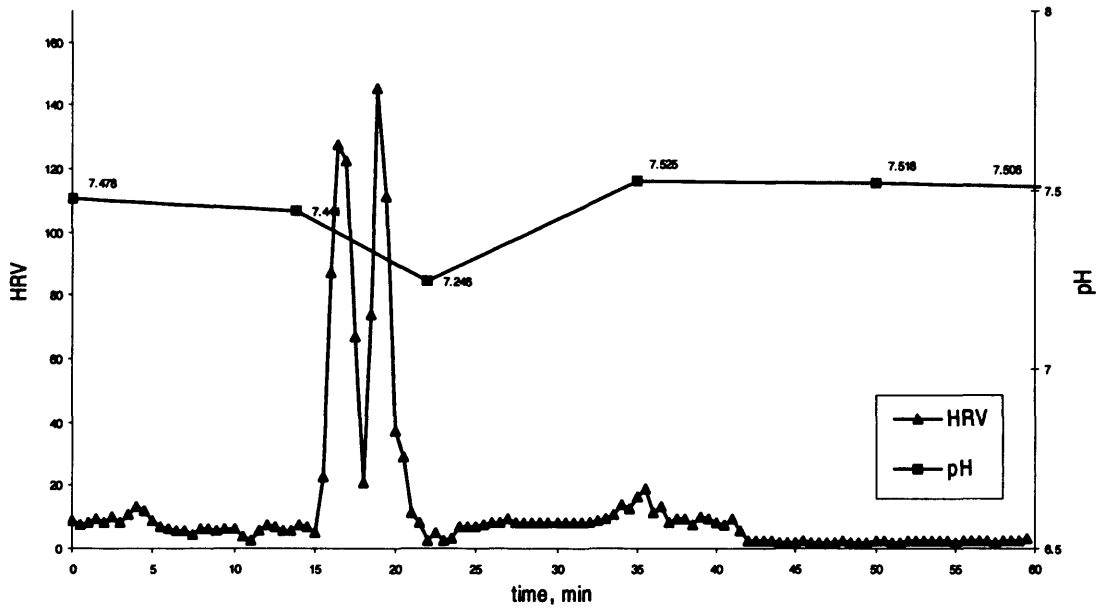


Figure 5.1: *Plots showing (a) heart rate against time and (b) heart rate variability against time for a single insult of asphyxia of duration 5 minutes (beginning at 15 minutes) and pH measured at regular intervals. Each point in (a) represents the average heart rate over 30 seconds and in (b) the standard deviation of NN intervals over 30 seconds. A marked decrease in heart rate and a large increase in heart rate variability occur from the onset of asphyxia to the end of the episode.*

In all cases the onset of asphyxia produced a marked decrease in heart rate (figure 5.1a) and a large increase in HRV (figure 5.1b), which continued throughout the period of asphyxia. Figures quantifying these changes are given in table 1; these show that the changes in HRV during asphyxia compared to beforehand are significant at $p < 0.05$. The measure of HRV increased several fold its original value for all asphyxic episodes greater than 1 minute.

Table 5.1: *Mean ±1sd for HRV and pH compared to the baseline level and mean ±1sd for neuroscore (NS); the significance of these results compared to the control group. ('not sig' is not significant)*

Duration	HRV (during/baseline)	p	NS (after)	p	pH (after/before)	p
1 min	8±5	0.04	74±5	not sig	1.001±0.009	0.006
3 min	46±28	0.001	75±2	0.04	0.981±0.003	0.005
5 min	63±30	0.01	60±9	0.01	0.976±0.007	not sig
7 min	80±22	0.03	48±11	0.04	0.974±0.001	0.01

The increased variability during the asphyxic episodes includes frequencies higher than the ventilation frequency (figure 5.2). The pH decreased after asphyxia with a more marked change for longer episodes (figure 5.3) and the correlation between the changes in HRV and pH can also be seen in figure 5.1b).

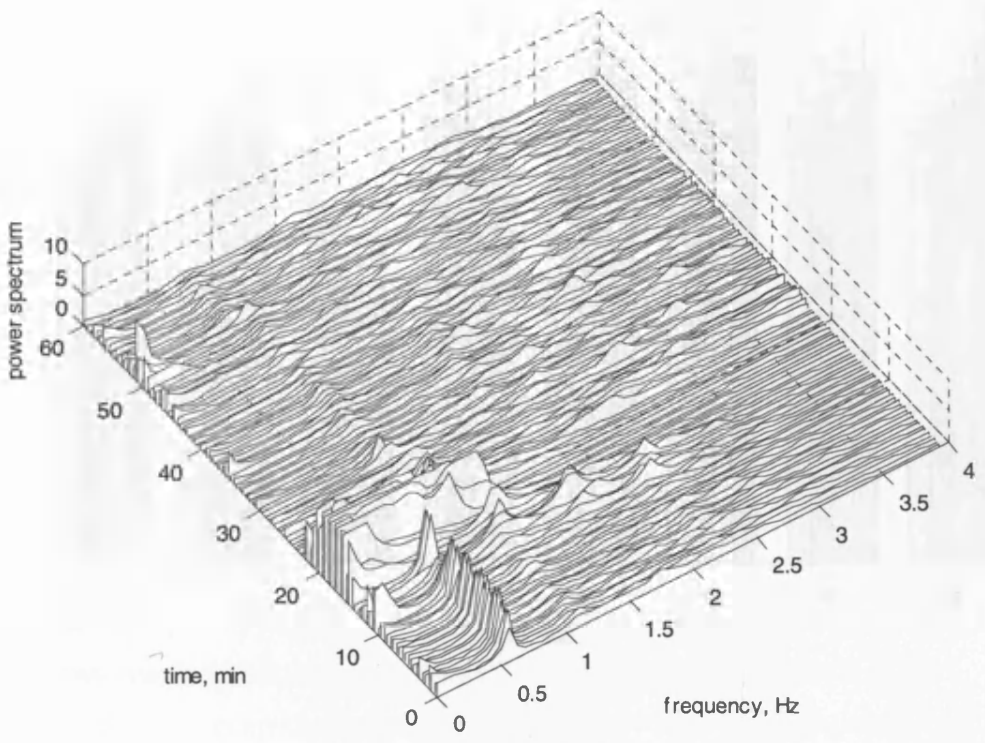


Figure 5.2: *Power spectra of a rat submitted to 5 minutes of asphyxia (beginning at 15 minutes). After asphyxia it can be seen that the RSA peak (at 1 Hz) is depressed compared with its amplitude before asphyxia (at 0.6 Hz). Its shift in frequency is due to a manual change in the frequency of the ventilator needed to stabilise blood pH. NB: Magnitude of spectra was capped at 10 arbitrary units to amplify the details.*

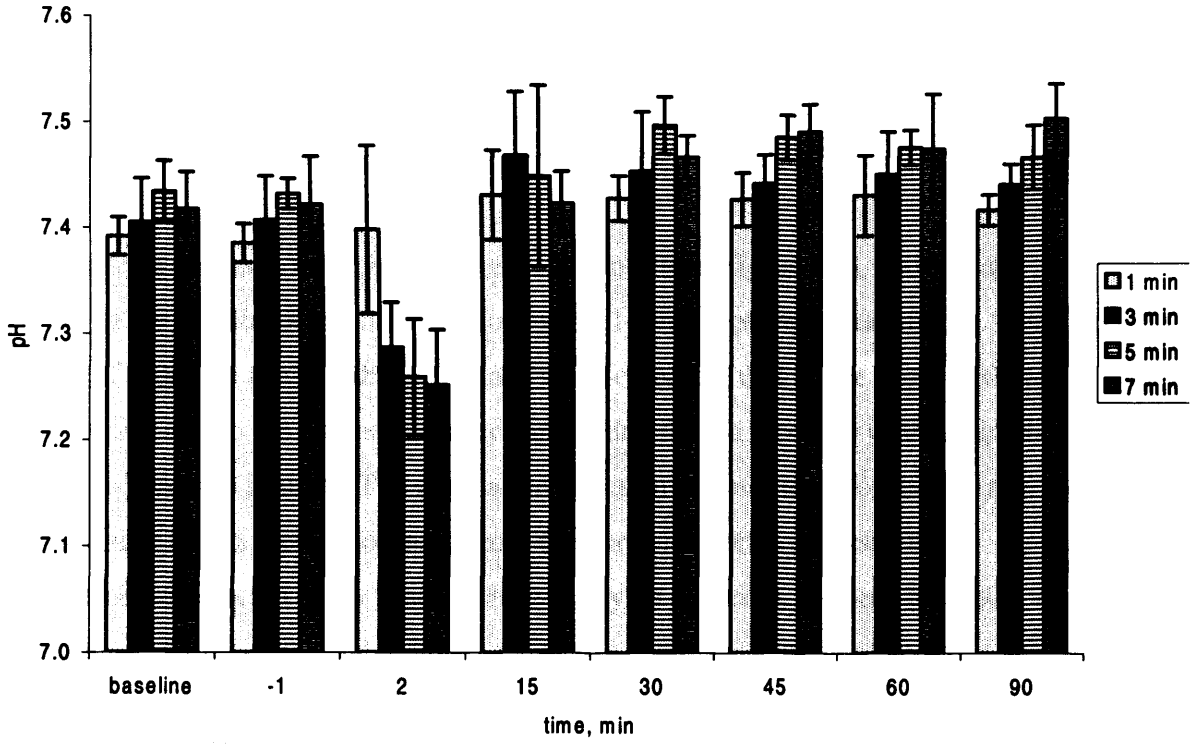


Figure 5.3: *Average pH for 1, 3, 5 and 7 minutes of asphyxia. These results are plotted against time relative to the asphyxia insult, hence -1 minute is 1 minute before the insult occurs and 2 minutes, is 2 minutes after the end of asphyxia. The error bars indicate one standard deviation.*

5.4.2 The resuscitation procedure

After asphyxia via airway obstruction, resuscitation was initiated by unclamping the tracheal tube and, for 3, 5 and 7 min of injury (but not for 1 min) an injection of adrenaline and mechanical ventilation restarting with 100% O_2. This ventilation procedure stops the pH levels falling too far but does not confound the pH readings and interpretation, rather minimises the largest changes in pH. The pH levels following asphyxia behaved as expected with a more marked drop for longer asphyxic episodes (figure 5.3), these changes were shown to be significant for asphyxia durations of 1, 3 and 7 minutes (table 5.1). The levels of carbon dioxide, which were

also measured but not shown here, also give the same qualitative information (higher rise for longer episodes).

5.4.3 Changes which occurred following asphyxia

The long term analysis, using histograms of the intervals (figure 5.4), showed an increase in the lengths of the intervals following 1 minute of asphyxia; after 3, 5 and 7 minutes of asphyxia the lengths of the intervals decreased, that is, the heart rate was higher, this is due to the adrenaline injection needed for the recovery of the animals after the 3-7 minute injuries. The adrenaline injection was not used for the 0-1 min cases. Similar trends were also found from the very short-term analysis using Poincaré phase plots: in many cases, before asphyxia occurred, the beat-to-beat pattern formed a diagonal line indicating a steady beating rate without sudden changes in beat length. Following asphyxia for the longer injuries, most beats were focused at a shorter beat length which may indicate a change in balance of the action of the sympathetic and parasympathetic tone; there was some scatter occurring also.

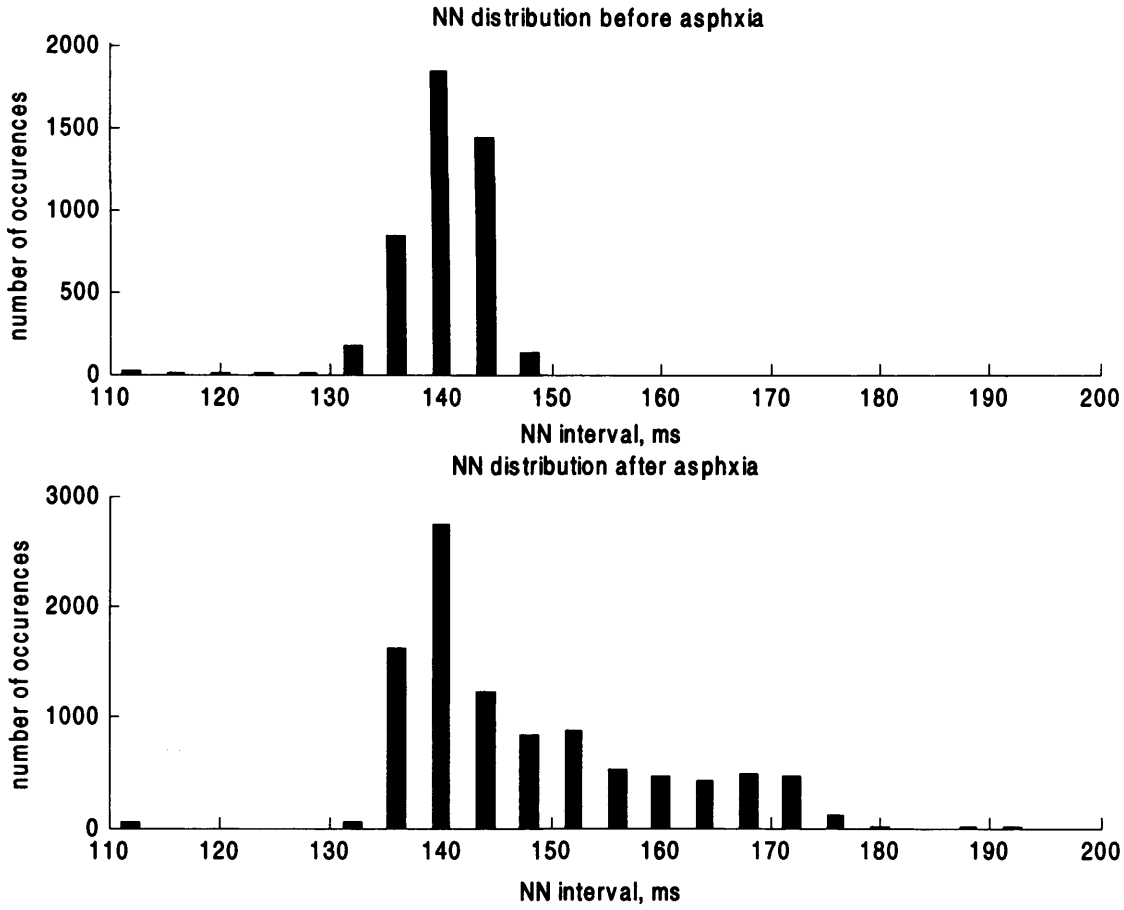
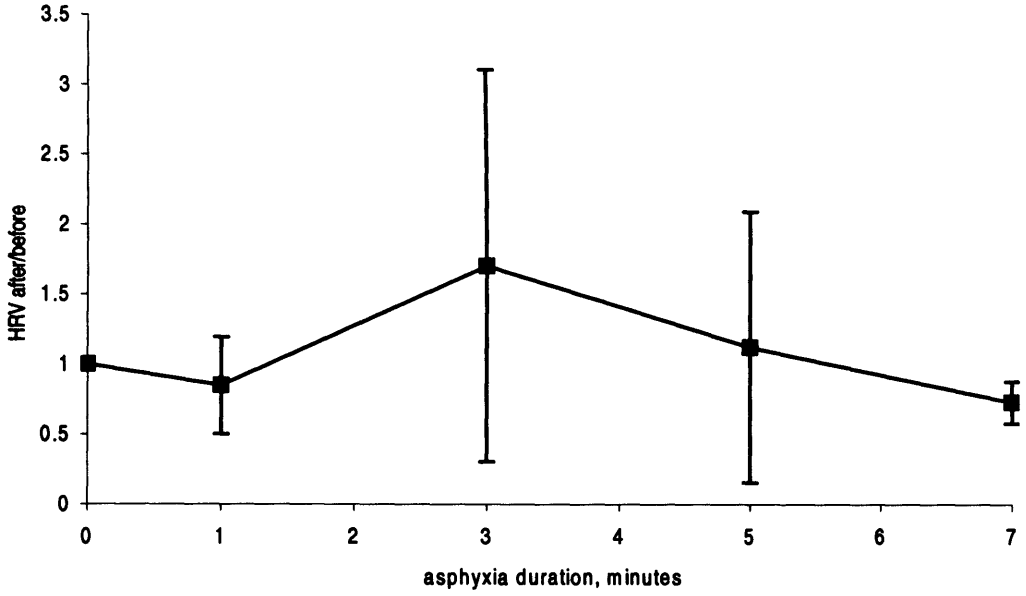


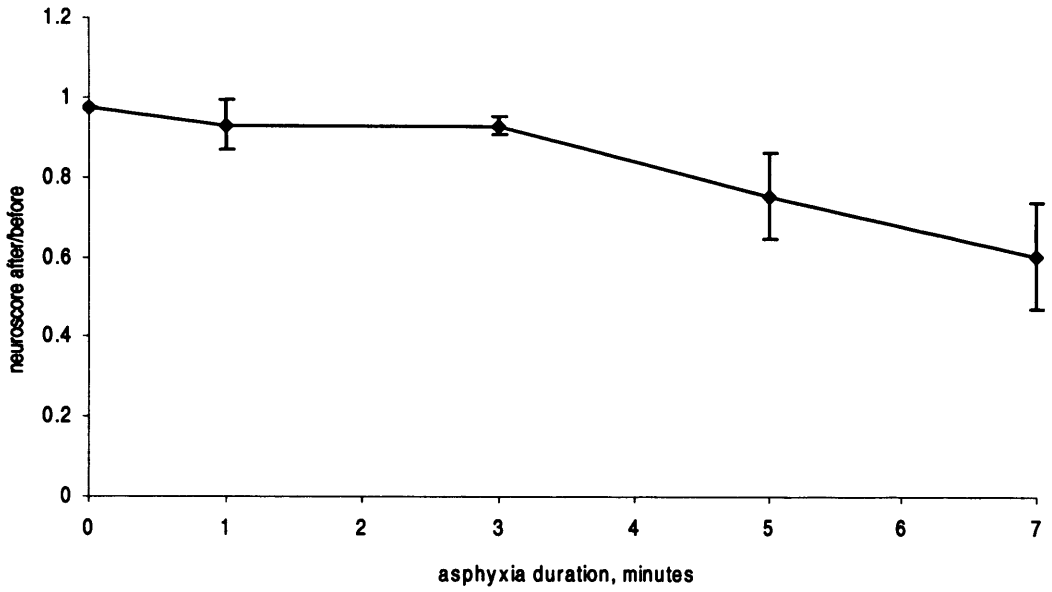
Figure 5.4: *Plots showing the distribution of NN intervals before and after 1 minute of asphyxia for one experiment. A wider spread of NN intervals, which are longer than those before asphyxia, result. No adrenaline was used in resuscitation following 1 minute insults.*

The graph given in figure 5.5a shows the change in the variability after asphyxia compared to before asphyxia; it can be seen that this ratio is unchanged for asphyxia duration of 1 minute, increased for duration of 3 minutes and decreased from this value for longer periods.

(a)


3.5
3
2.5
2
1.5
1
0.5
0
HRV after/before
0
1
2
3
4
5
6
7
asphyxia duration, minutes

(b)



b

Figure 5.5: *Plot showing (a) HRV and (b) neuroscore ratios of values after asphyxia divided by those before, against the duration of asphyxia. Error bars in each case indicate 1 standard deviation. The behaviour of HRV is interesting and is discussed in the text. The neuroscores monotonically decrease for increasing durations of asphyxia.*

The neuroscore index decreases monotonically for increasing lengths of asphyxia, as expected (figure 5.5b), this was found to be significant for 3, 5 and 7 minutes of asphyxia. The comparison of HRV, neuroscore and pH for the different durations of asphyxia (figure 5.6) shows a separation between the shorter (0, 1 and 3 minute) and longer (5 and 7 minute) lengths of insult.

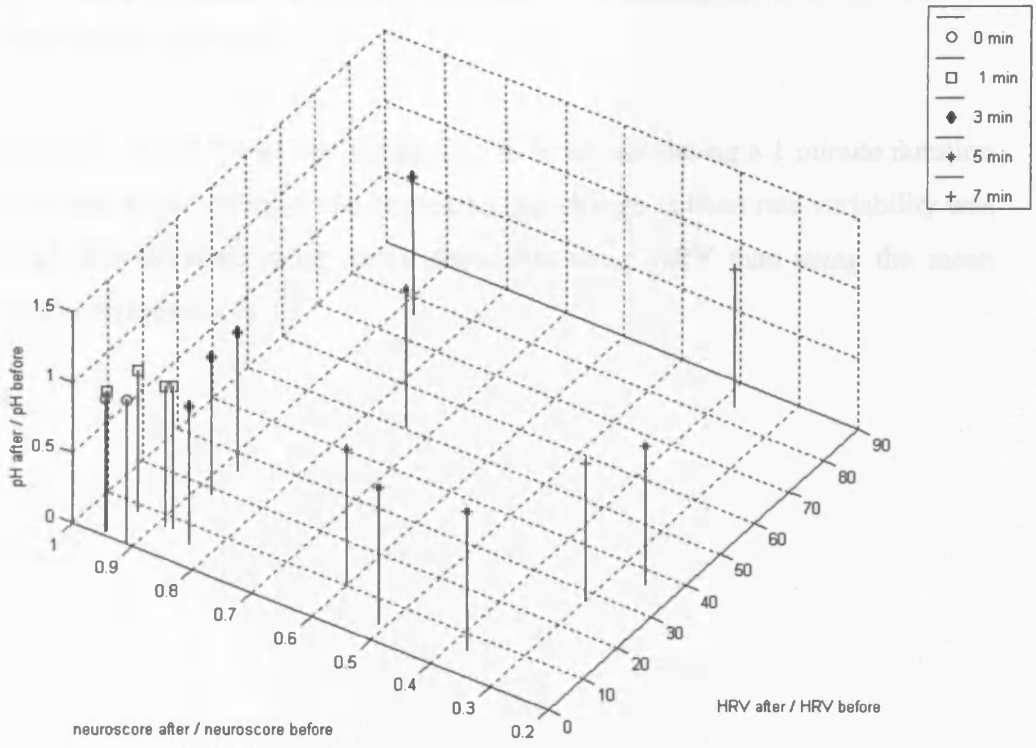


Figure 5.6: *The correlation between HRV, neuroscore and pH indices for the 0, 1, 3, 5 and 7 minutes of asphyxia. Each index is calculated from the mean value for that quantity after asphyxia divided by the mean of that value before. A clear separation between the short (0, 1, 3) and long (5, 7) lengths of asphyxia is seen.*

5.5 Discussion

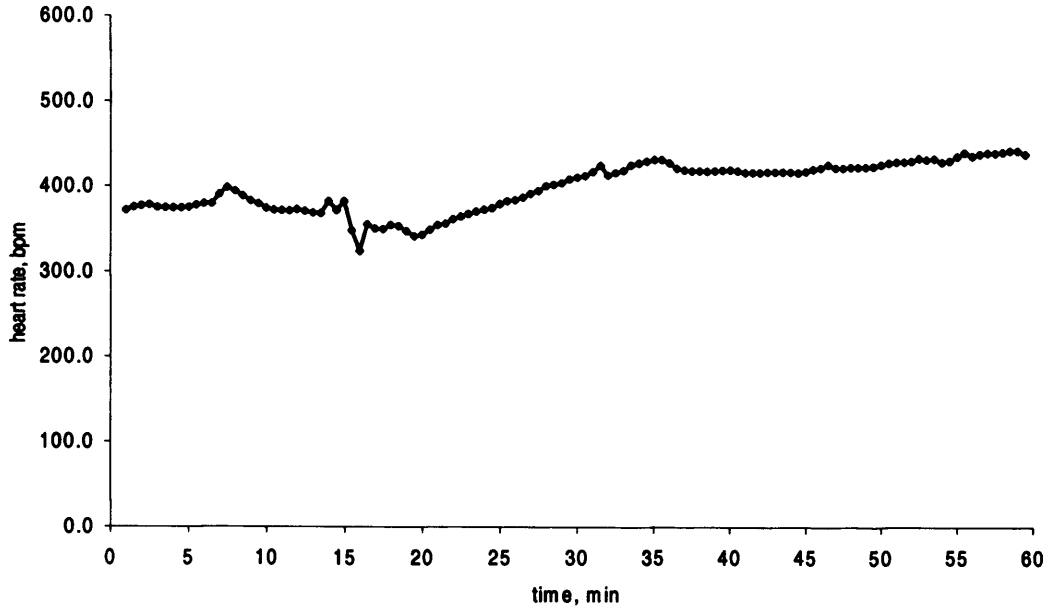
5.5.1 Detecting asphyxia while it is occurring

It has been confirmed that the onset of asphyxia has a great effect in depressing heart rate which is part of the well-known 'diving response' widely found to occur in both humans and animals (Heath and Downey 1990). There is also a dramatic change in HRV which was found to occur in all cases here, for all durations. If the shape of the HRV graph is looked at closely, a dip after the initial peak can be seen in both figures

5.1 and 5.7 which emphasises that HRV is a measure of modulation of autonomic tone, rather than of tone itself.

In two instances it was found that the change in heart rate during a 1 minute duration of asphyxia was small, however the corresponding change in heart rate variability was rather large and therefore more easily detectable using HRV than using the mean heart rate alone (figure 5.7).

(a)



(b)

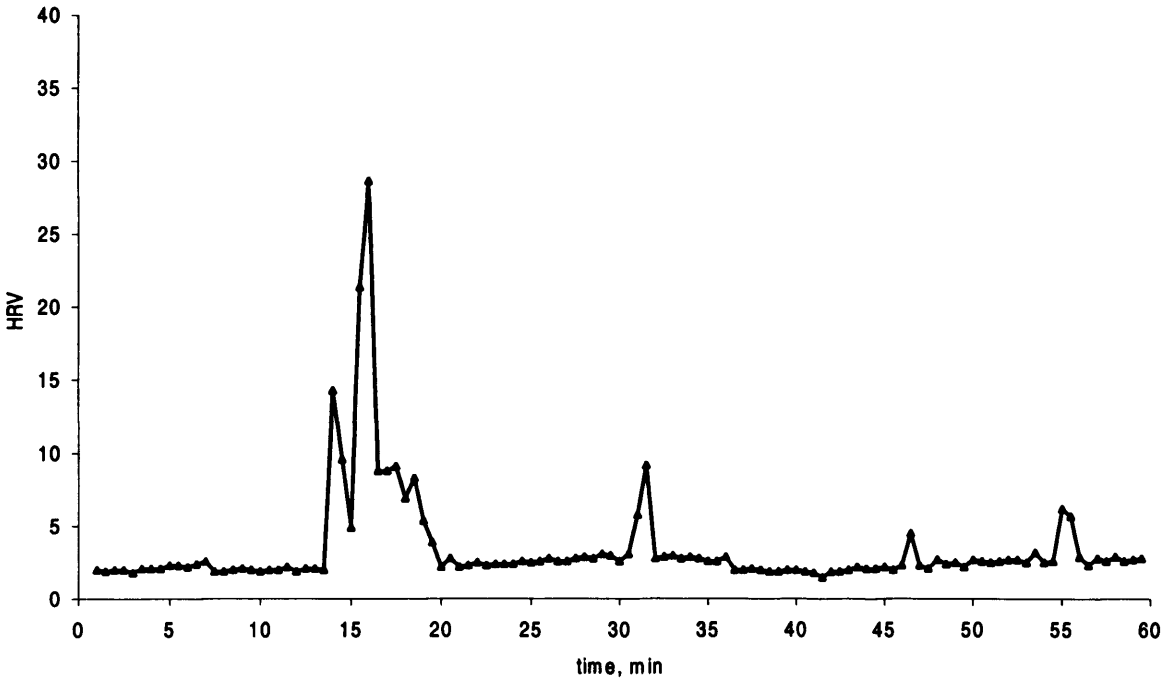


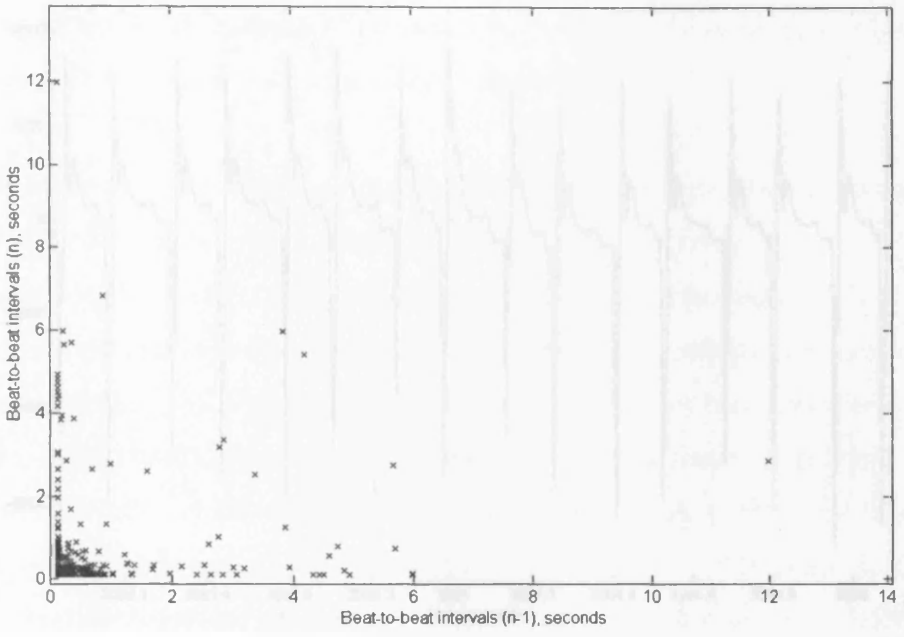
Figure 5.7: *The heart rate (a) and heart rate variability (b) plotted against time before, during and after asphyxia of duration 1 minute (starting at 13.5 minutes). The change in heart rate at the onset of asphyxia is not as well defined as the increase in heart rate variability.*

A dramatic increase in spectral power during asphyxia also occurred, indicating a change in sympathetic and parasympathetic control; in most cases the original spectral pattern was resumed following asphyxia but occasionally the peak at the respiratory sinus arrhythmia (RSA) frequency was depressed (figure 5.2). This correlates with previous studies where a decrease in the RSA component in comparison to controls was found for infants who had suffered from asphyxia (Divon *et al.* 1986, Anninos *et al.* 2001).

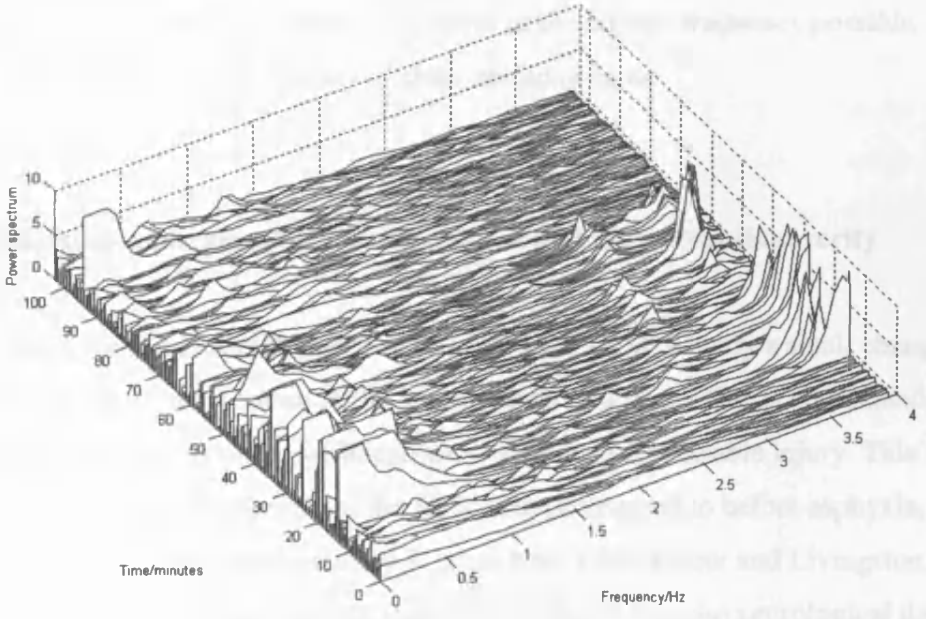
From experience, time-domain methods are very useful for detection of the onset of the asphyxic episode and the extra investment in computational effort to show spectral analysis is only worthwhile if it can show interesting events that are not detectable (or easily characterised) using time-domain methods. One such event that happened in one of the experiments is the presence of 'alternans', when a short RR interval is followed by a long one and this pattern of short-long-short-long intervals repeats itself. In this case the time-based analysis just flags that there is a high variability without pointing to the presence of 'alternans,' (figure 5.8a) while the spectrum clearly shows a very marked peak at half the heart rate which is the highest frequency in the spectrum (figure 5.8b). A segment of ECG for this record, which shows this beating pattern, is given in figure 5.8c

Significant changes in pH levels following asphyxia occurred for most injuries, meeting expectations. Following a 1 minute episode, only slight changes in the level of pH was seen, which suggests that i) 1 min asphyxia is not a serious insult and ii) pH is not as sensitive to asphyxia as our measure of HRV has been shown to be.

(a)


Beat-to-beat intervals (n), seconds
Beat-to-beat intervals (n-1), seconds
0
2
4
6
8
10
12
14

(b)


Power spectrum
Time/minutes
Frequency/Hz
10
5
0
100
90
80
70
60
50
40
30
20
10
0
0
0.5
1
1.5
2
2.5
3
3.5
4

(c)

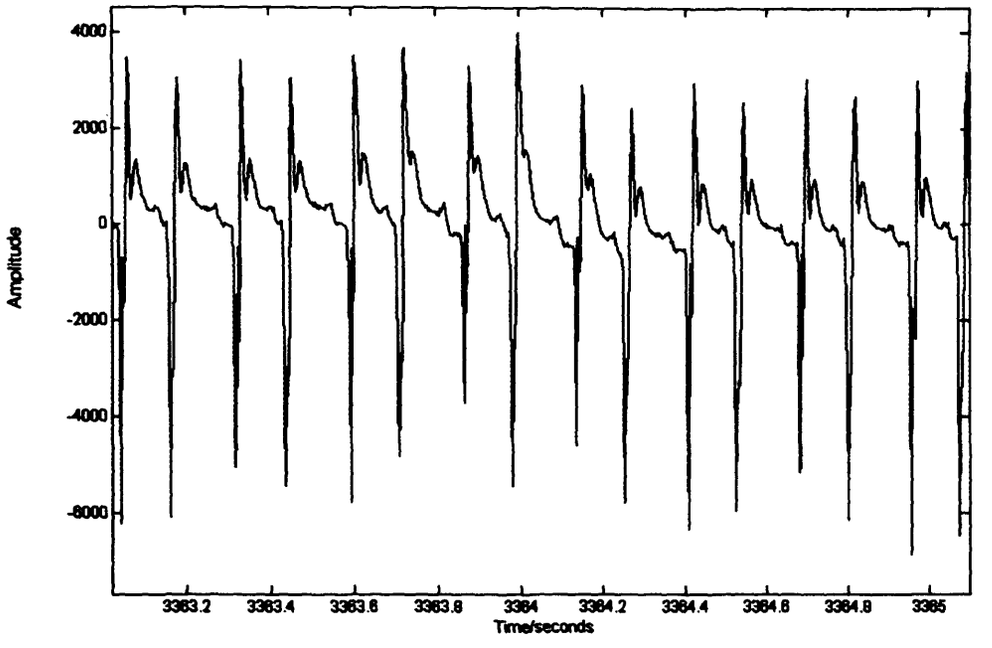


Figure 5.8: *(a) shows an irregular Poincaré plot from a rat who had consecutive short and long heart beats. The power spectrum (b) allows this pattern to be identified more easily with the existence of a component at the highest frequency possible. (c) A section of ECG showing this series of short and long beats.*

5.5.2 Detecting asphyxia after it has occurred and estimating its severity

The findings for the 1-minute duration of asphyxia tests show only a small change in heart rate giving some increase in the lengths of the intervals. This is understandable: 1 minute of asphyxia is not a sufficient time to produce appreciable injury. This idea is confirmed by the overall ratio of the HRV after, compared to before asphyxia, which was found to be approximately 1. It has been noted (Parer and Livingston, 1990) that the incident must be prolonged and profound to cause neurological damage and that following minor or brief periods this simply does not happen.

Hendrickx *et al.*, (1984) used a neurological deficit scoring system for their investigation into the recovery of rats from asphyxia and found some correlation

between the duration of the asphyxia and the neurological deficit score but discounted the results due to the amount of scatter present. In this work it was found that as the period of asphyxia was increased from 3 to 5 to 7 minutes, the neurological score monotonically decreased, with little scatter (figure 5.5b).

The behaviour suggested by the results for HRV after compared with before the insult is interesting and can be summarised thus: for 3 min of asphyxia HRV(after)>HRV(before) (1.7 times larger), suggesting that the asphyxia is a disturbance that challenged the control mechanisms which modulate the heart rate and they are responding and adapting to the insult by changing the heart rate; for 5 min of asphyxia, HRV(after)>HRV(before) too, but only 1.2 times larger, while for 7 min of asphyxia HRV(after) < HRV before, suggesting that for 7 min of asphyxia the control mechanisms which modulate the heart rate became depressed or damaged. Both the pH and neuroscore indices are lower for longer lengths of asphyxia, also implying a greater effect on the system following the more serious injury. The number of experiments conducted here was not large and the standard deviation for the HRV was rather more than anticipated, so the above interpretation needs confirmation from studies with more subjects.

The above interpretation ties in with lower variability occurring after the longer periods of asphyxia. Geocadin *et al.*, (2000) also show and discuss the correlation between duration of asphyxia and neurological score for this animal model. It is thought that neurones become injured following 3-5 minutes oxygen deprivation; a marked decrease in the neuroscores of rats asphyxiated for 5 minutes compared to the rats asphyxiated for 3
minutes was found.

5.6 Conclusions

The main conclusion is that short-term HRV as defined here (standard deviation of NN intervals using 30 s frames) is a very sensitive indicator of asphyxia. A large increase in this parameter occurred at the onset of the asphyxic episode in all

experiments. Further work is needed to measure and study specificity since it was noted that instances of increases in HRV without asphyxia occur, especially during some experimental procedures such as sampling blood for blood gases analysis.

Other changes were also found to occur, such as the expected decrease in heart rate during asphyxia and a decrease in pH levels during and immediately after asphyxia, however these were not as pronounced as the change in HRV.

The effect of a long duration of asphyxia was a reduction in variability following, compared with its value before the episode, which suggests neurological damage and may be useful in estimating the severity of the asphyxia once it has occurred.

It was noted that 1 minute of asphyxia is not a sufficient injury time to cause some of the changes listed above to occur, but a clear indication of even these minor asphyxic episodes could still be detected using HRV.

The potential of using this short-term measure of HRV for the detection of fetal distress will be explored further in chapter 7.

6.0 Doppler ultrasound

6.1 The Doppler effect

This was first noted by Christian Johann Doppler in 1842 who found that when a stationary source emits a signal at a constant frequency an observer moving relative to this source observes a change in frequency of the signal. The same is true when the observer is stationary and the source is moving. When both the observer and the signal source are stationary but the signal is reflected from a target that is moving relative to the observer and signal source there is similarly a change in the observed frequency of the ultrasound when it is returned to the receiver. (Burns 1987, Evans 1988, Evans and McDicken 1989). An ultrasound signal of known frequency is used to insonate a blood vessel. When the signal hits the red blood cells in this vessel, which are much smaller than the wavelength of the ultrasound, it is scattered back to the transducer at a different frequency. This change in frequency is known as the Doppler shift (Burns 1987).

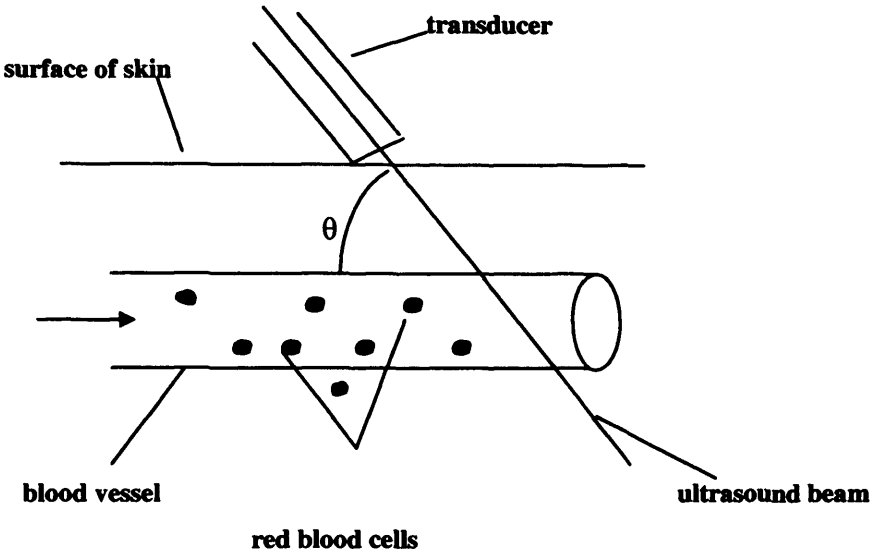


Figure 6.1: *Diagram shows an ultrasound beam hitting red blood cells in a blood vessel and scattering the ultrasound beam back to the signal transducer. (Adapted from Evans 1988).*

The Doppler shift frequency can be found from equation 6.1, by subtracting the frequency of the reflected signal f_r from the frequency of the transmitted signal f_t.

$$f_d = f_t - f_r = \frac{2Vf_t \cos\theta}{c} \qquad (6.1)$$

where V is the velocity of the target, c the velocity of ultrasound in blood and θ the angle between the ultrasound beam and the direction of motion of the blood cell (Evans 1988).

The frequency f_d lies within the audible range and although, to those experienced in listening to Doppler audio signals this can provide useful information, it is usual to process the signal further.

6.2 Analysis of Doppler ultrasound signals: Frequency demodulation

From equation 6.1 it can be seen that the Doppler frequency (f_d) is directly proportional to the velocity of the moving target, the blood cell. In an ideal blood vessel with laminar flow the velocity profile of the blood cells will be parabolic, as shown in figure 6.2, where the fastest flowing blood cells will be in the centre of the vessel and the slowest blood cells at the vessel wall. Those blood cells at the centre of the flow will produce the highest Doppler frequencies.

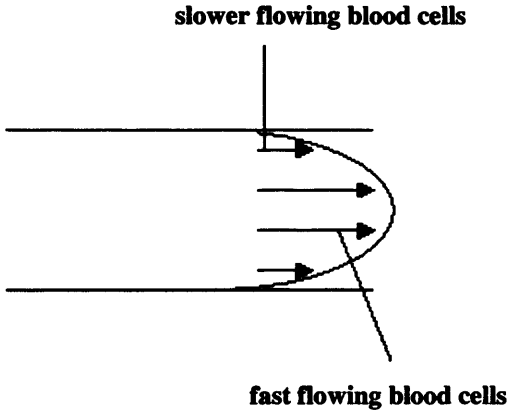


Figure 6.2: *Laminar flow in an ideal vessel; arrows represent velocity of blood cells.*

For parabolic flow in an ideal vessel the distribution of the velocities of blood cells will be rectangular since there will be the same number of fast flowing blood cells as slower ones. In practice this distribution tends to be skewed due to a non-parabolic flow profile, the non-uniform insonation of the blood vessel and spectral broadening (Evans and McDicken 1989). Spectral broadening arises due to the assumption in equation 6.1 that the ultrasound beam is of unit width and therefore only one angle results from the inclination of the beam to the blood vessel; in practice a range of angles exist which gives rise to spectral broadening. This is shown in figure 6.3.

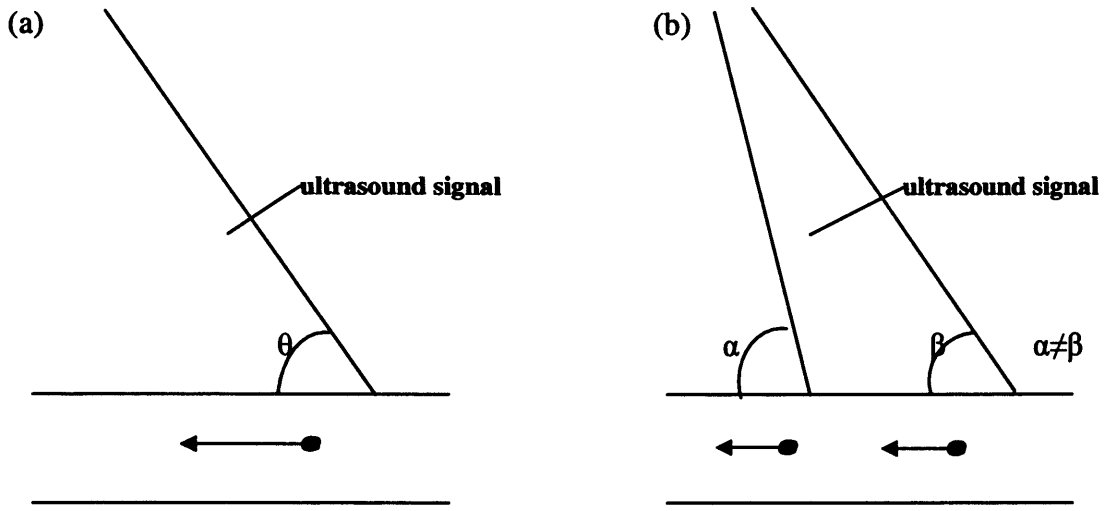


Figure 6.3: *Spectral broadening occurs due to the angle the ultrasound beam makes with the surface changing across the width of the beam. (a) shows the ideal situation where the beam is of unit width; (b) shows the real situation where the angle changes due to the beam width; this is not included in the Doppler shift equation.*

The velocity of the blood cells is proportional to the frequency shift, this distribution of velocities of the blood cells or frequencies can be displayed using power spectral analysis, as shown in figure 6.4.

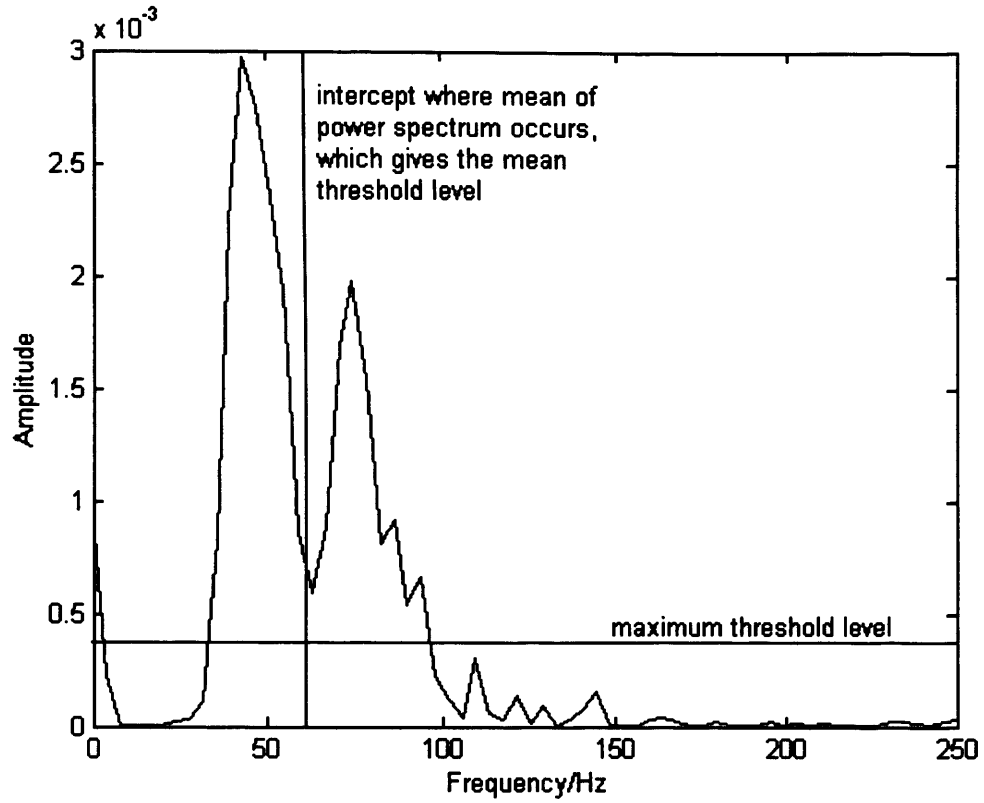


Figure 6.4: *Power spectral analysis of 128 samples of blood velocity signal with examples of two threshold levels, which could be used for envelope determination: the mean frequency and the maximum frequency envelope.*

Two points in this power spectrum are easily identified: the mean of the spectrum and the point where the maximum frequency occurs and both are indicated in figure 6.4. The envelope signal is derived from consecutive power spectra. In producing the envelope signal a set of blood cells are tracked and it is usual to track either those flowing at the mean velocity or those flowing at the fastest velocities, which correspond to the mean and maximum thresholds as plotted. Evans *et al.* (1989) showed that noise is not as problematic if the fastest flowing scatterers are tracked and so this will be used here.

A series of these power spectra for consecutive segments of signal produces a sonogram (figure 6.5). Each vertical line of the sonogram is one of these power spectra and the envelope signal which gives the profile of the maximum velocity of the blood cells is superimposed onto the sonogram.

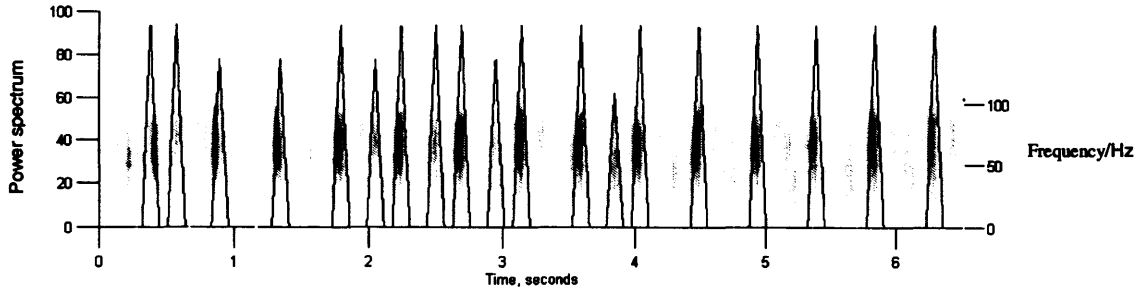


Figure 6.5: *A sonogram plot for 8 seconds of data with the envelope signal superimposed on top of the sonogram.*

6.3 The Doppler transducer

The transducer is the device which converts electrical energy to acoustic energy and acoustic energy back to electrical energy. Often, as in this application, the transducer both transmits and receives the ultrasound signal. Quartz or a piezoelectric ceramic is used in the transducer: when a voltage is applied perpendicular to the crystal it causes the crystal to vibrate and this produces a sound wave. Conversely when a pressure wave impinges on the transducer it generates a voltage (Evans and McDicken 1989, Zagaebski 1996).

6.4 Pulsed Doppler

Doppler instruments use either continuous wave or pulsed wave ultrasound (Evans and McDicken 1989). The HP8040A cardiotocograph, which will be discussed further in the next chapter, uses pulsed wave ultrasound for recording fetal heart rate before and during labour. The pulsed wave system works by emitting short bursts of ultrasound at set intervals and then, following reflection (or scattering), receiving these signals back at the transducer for a short period of time, before restarting this cycle. The time required for the signals to be received at the transducer depends on the depth of the reflecting (or scattering) target. The ultrasound frequency used by the HP8040A machine is 1.024MHz.

6.5 This work

Fetal heart rate data can be obtained using an HP8040A cardiotocograph from an internal scalp electrode or non-invasively obtained Doppler signals. Concentrating on the Doppler signals here, it was possible to obtain the Doppler audio signal and the machine derived Doppler envelope signal; it is intended to derive the maximum envelope from the audio signal and compare this with the machine derived envelope.

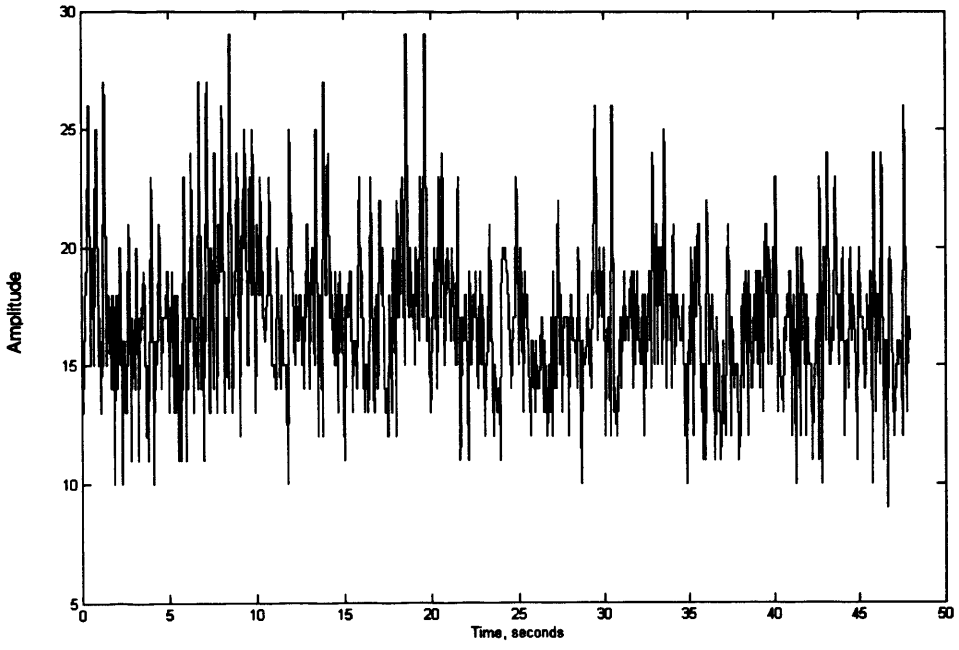
6.6 Methods

Six Doppler audio signals were obtained at a sampling rate of 2kHz using a data acquisition card and laptop connected to the HP8040A fetal heart rate monitor.

6.6.1 Frequency demodulation

The envelope was first derived using frequency demodulation which is where the envelope signal is extracted from the sonogram using the attribute of frequency: this method is given in section 6.2. The difficulty with this method is the choice of threshold level: too low a level and noise rather than signal is detected, whereas a level which is too high results in no point being detected and parts of the envelope signal being omitted.

(a)



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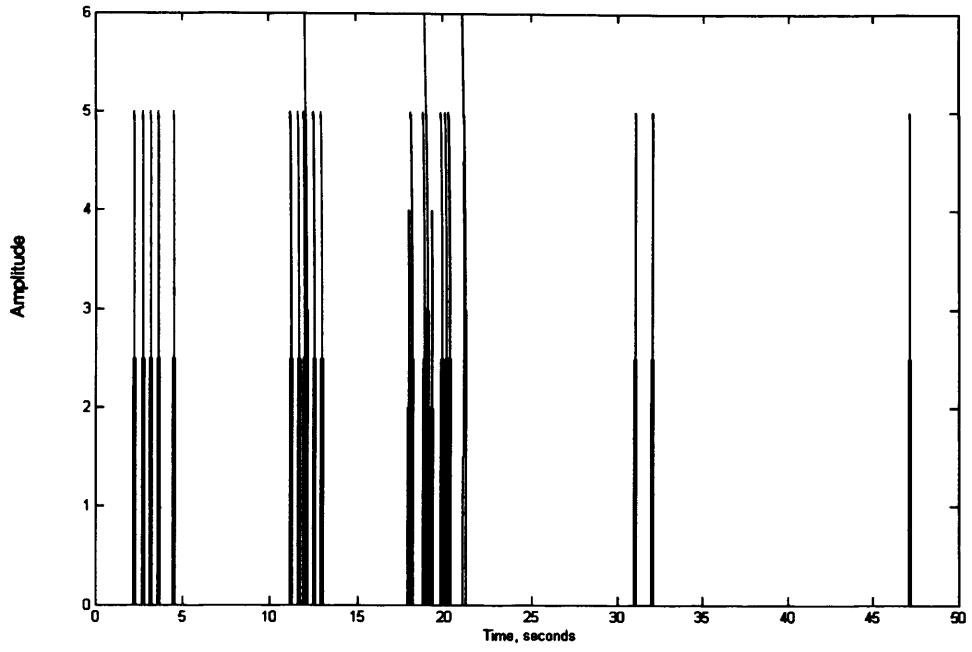


Figure 6.6: *(a) The envelope signal where the threshold was too low and (b) the envelope signal where the threshold was too high.*

In order to choose the optimum threshold level the work of Evans *et al.* (1989) was referred to. An initial low threshold was used to produce an envelope signal for five frames of data and the mean of each individual spectrum was calculated and then an overall average for the five spectra found. The threshold level was increased and this was repeated for different threshold levels. The results of the mean of the maximum envelope against the threshold level were plotted (figure 6.7) and where the graph becomes flatter, this was selected as the optimum threshold level. Fourier analysis with a Hanning window was used for finding the power spectrum.

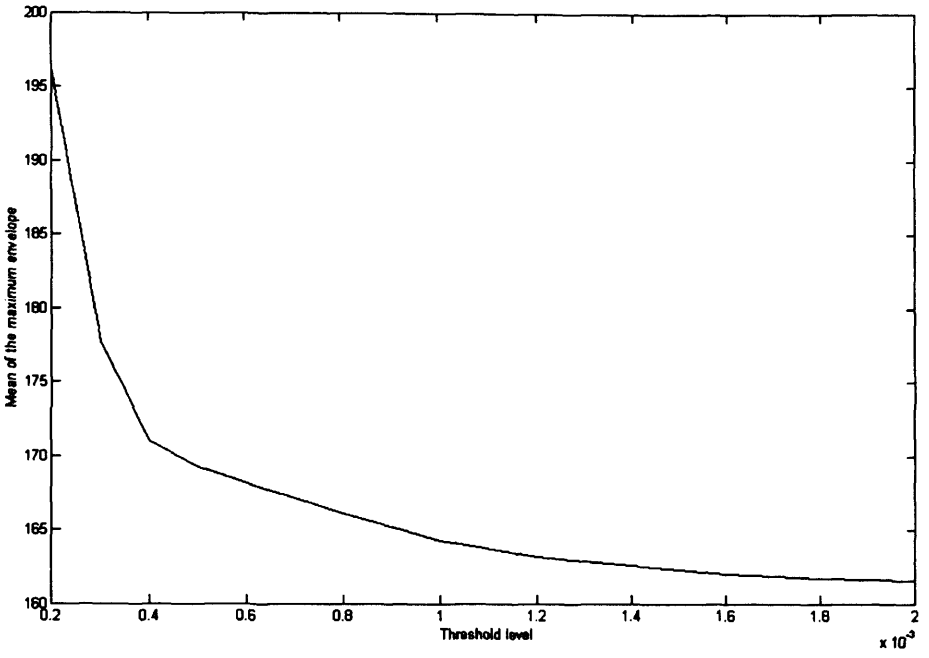


Figure 6.7: *A plot of the mean of the maximum frequency envelope for five frames of data against threshold level. The threshold level chosen here was 0.0012 since this is where the graph becomes more constant.*

The envelope produced in this way is different from that produced by the cardiotocograph, since the cardiotocograph uses amplitude rather than frequency demodulation to produce the envelope signal.

6.6.2 Amplitude demodulation

The HP8040A cardiotocograph machine uses amplitude demodulation for the processing of the Doppler audio signal. This works on the assumption that the amplitude and frequency of the signal are linearly dependent thus the amplitude demodulation should give similar results to the frequency demodulation.

When Doppler ultrasound insonates a blood vessel the signal is reflected by the blood cells but also by the moving vessel wall. This produces a Doppler shift at a low frequency because the vessel wall is moving slowly. By using a high pass filter this

frequency component known as vessel wall thump, is eliminated. The linear region of the frequency response for this filter gives the linear relationship between the frequency and amplitude of this signal.

Both machine derived envelope and Doppler audio signals are high-pass filtered to get rid of the vessel wall thump component and then to produce the envelope signal by amplitude demodulation, the signal is rectified and low pass filtered. Here a simplified method of amplitude demodulation will be used.

Looking at the raw audio signal given in figure 6.8, the peaks which occur in the signal are the points where the velocity of blood is at its quickest, which is immediately after a heart beat. Since it is the time taken between beats which is of interest in this work, by using an adaptive threshold these peaks can be detected and the intervals found.

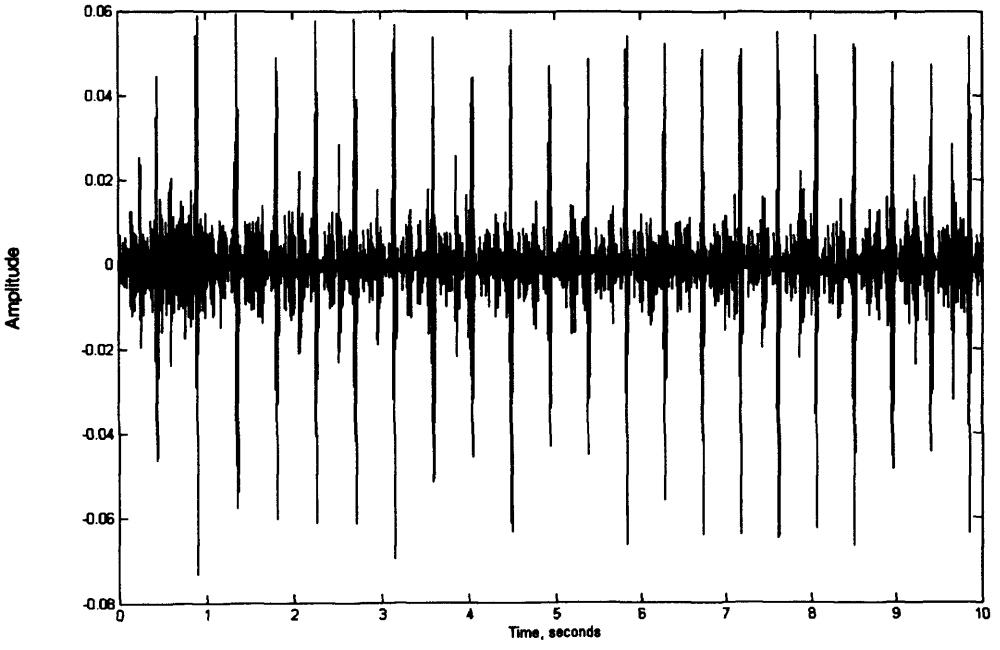


Figure 6.8: *A section of raw Doppler audio signal.*

6.7 Results

The information which can be derived from the envelope signals is the important quantity here, so the beat-to-beat intervals of the envelope signals found from the frequency and amplitude demodulations of the Doppler audio signal will be compared to those intervals derived from the machine produced envelope signal. Figure 6.9 shows the beat-to-beat intervals from the machine obtained envelope signal with noise elimination (explained further in chapter 7).

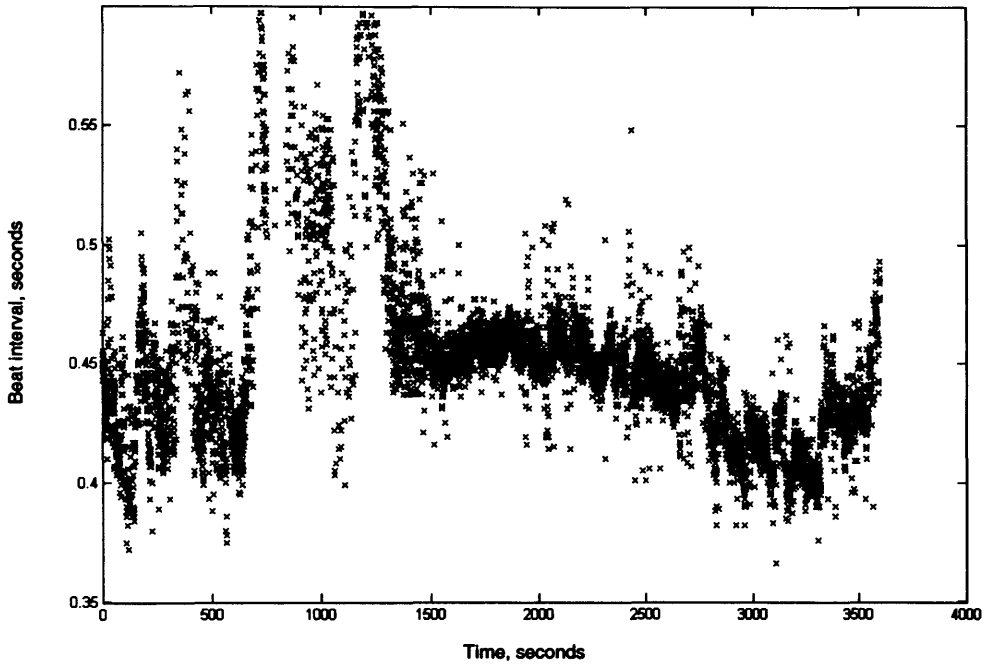


Figure 6.9: *Beat-to-beat intervals detected from the machine derived envelope signal.*

6.7.1 Results from the frequency demodulated signal

A frame of length 128 samples was chosen since it is long enough to allow Fourier analysis to be performed but short enough that a reasonable envelope sampling frequency can be obtained. Tests using frame lengths of 256 were performed. For 256

samples the results were worse with little variability in beat-to-beat intervals evident from the plot of intervals.

The first set of results from the Doppler audio signal presented here used frames of 128 samples and the optimum threshold level was found to be 0.001. The plot of the intervals (figure 6.10) derived from the beat detections shows low resolution which is due to the resulting sampling frequency of the envelope signal being just 15.5Hz.

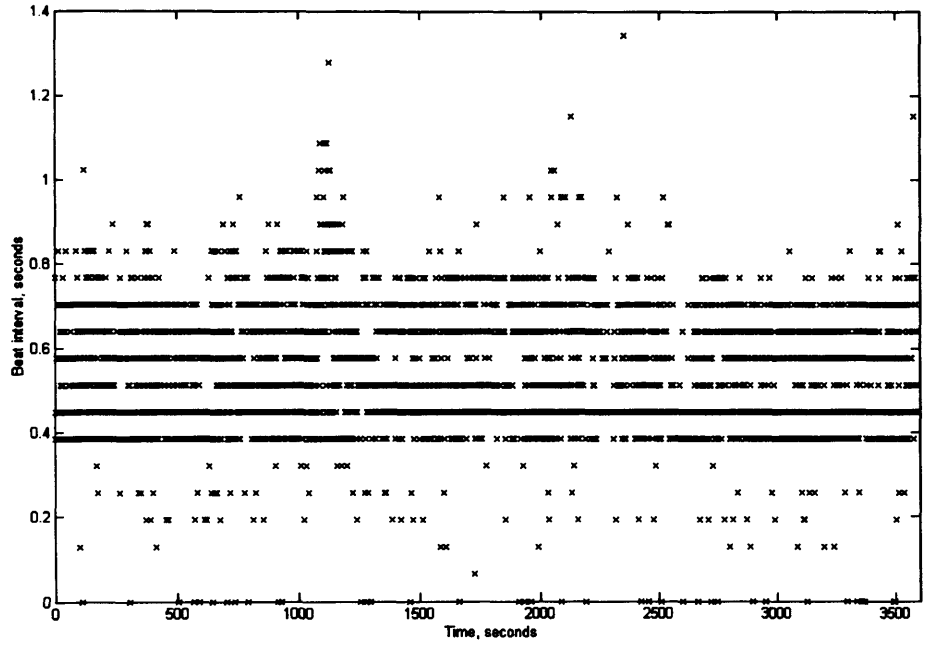


Figure 6.10: *Plot of the intervals obtained from the envelope signal resulting from the analysis of the Doppler ultrasound signal for a frame length of 128 samples.*

The beat intervals are plotted in separate distinct bins which is due to the low sampling frequency of the resulting envelope signal. To try to overcome this problem with resolution it was decided to overlap the frames of signal before power spectral analysis. Figure 6.11 shows the intervals found from overlapping the signal by 75% (32 new samples per frame) and figure 6.12 shows the results from overlapping by 93.75%, 8 new samples per frame.

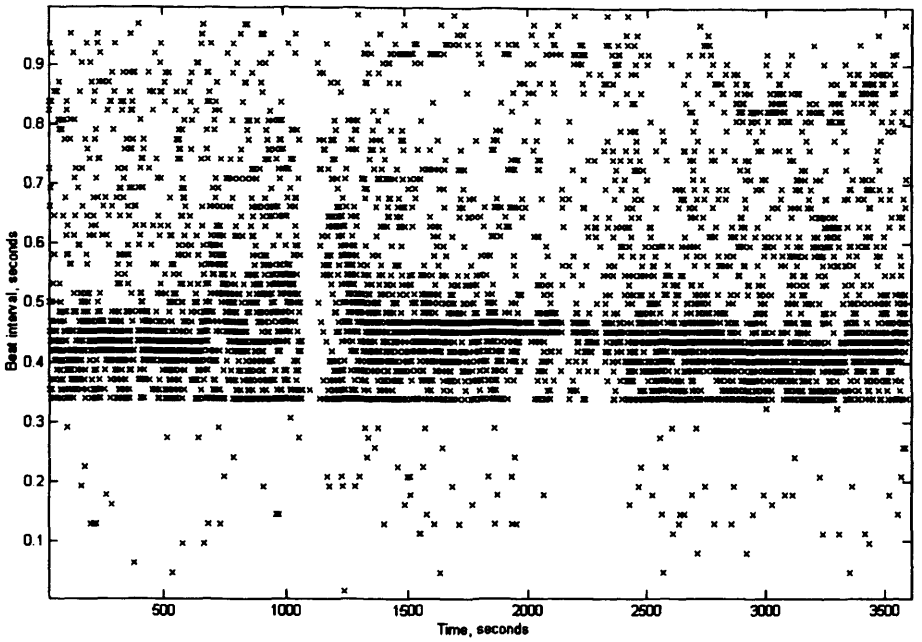


Figure 6.11: *The beat-to-beat intervals measured from the Doppler envelope signal formed by overlapping the audio signal by 75%.*

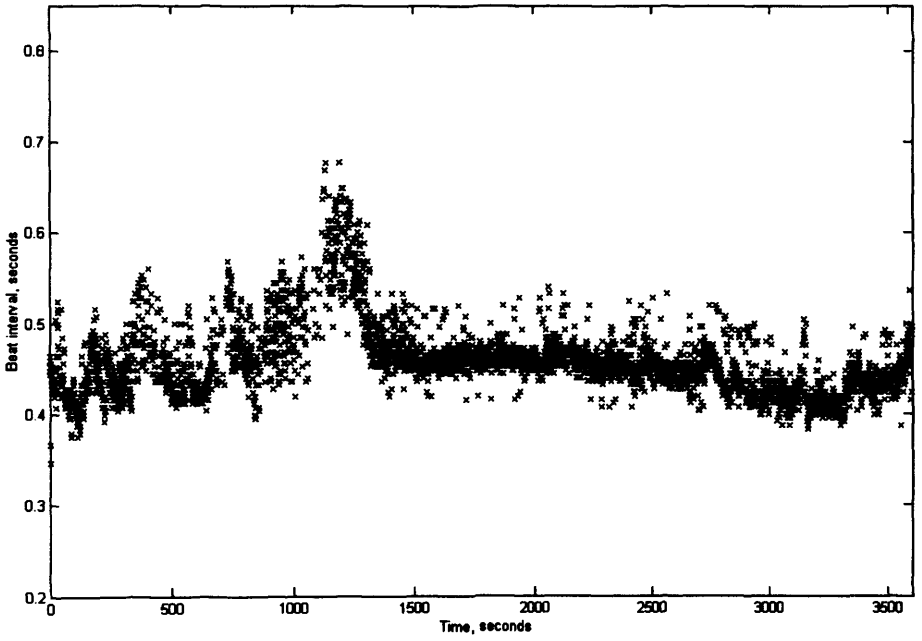


Figure 6.12: *Beat-to-beat intervals achieved when frequency demodulation of the Doppler audio signal was performed using frames containing 128 samples overlapped by 93.75%.*

By overlapping the signal, the problem with the low resolution improves and some variability in the intervals can be seen. Slight improvements in resolution were made using frames containing 64 samples overlapped by 93.75%.

6.7.2 Results from the amplitude demodulated signal

The beat-to-beat intervals from the envelope signal found using amplitude demodulation, are compared to those obtained from the machine derived envelope signal in figure 6.13; both are plotted following noise elimination, which involves checking accelerations and decelerations according to RCOG guidelines and will be explained further in the next chapter.

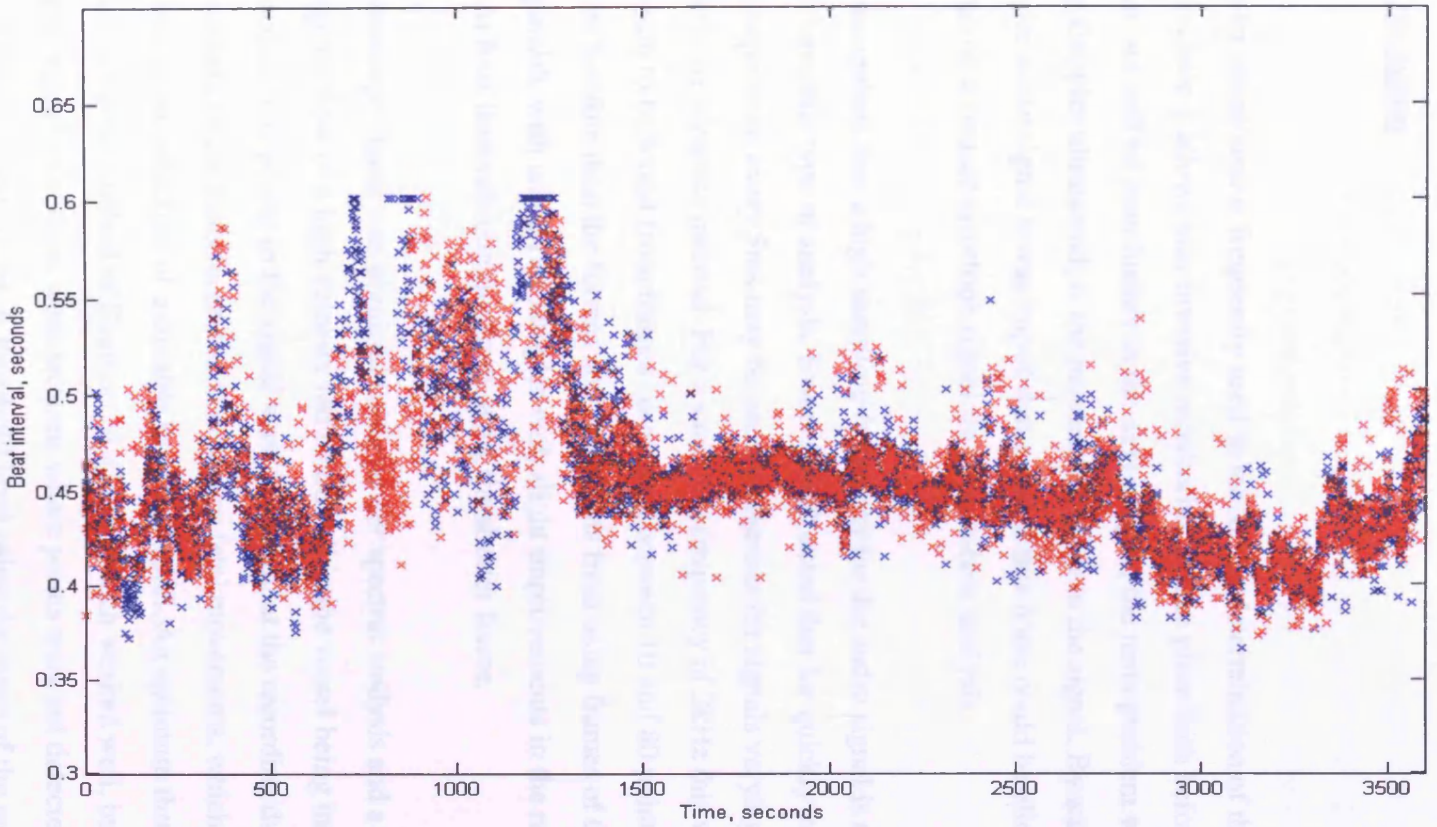


Figure 6.13: *A comparison of the beat-to-beat intervals from the raw audio signal (dark blue) and from the machine derived envelope signal (red).*

The resolution of the beat-to-beat intervals is 0.5ms which allows the variability in beat length to be seen. The results using this analysis compare well with the intervals detected from the machine produced envelope signal.

6.8 Discussion

Doppler ultrasound is frequently used in labour for determination of the fetal heart rate because it allows non-invasive monitoring to take place both before and during labour. As will be seen further in the next chapter, the main problem which exists in using Doppler ultrasound, is the presence of noise in the signal. By analysing the raw Doppler audio signal it was hoped that some of this noise could be eliminated thus producing a cleaner envelope signal for beat-to-beat analysis.

It is recognised that a high sampling frequency for the audio signal is needed in order to perform this type of analysis. Evans (1988) noted that for quickly varying signals, a power spectrum every 5ms may be needed whereas for signals varying more slowly, 40 ms is an adequate interval. For a sampling frequency of 2kHz this would require a spectrum to be found from frames containing between 10 and 80 points, the latter case is more feasible than the former and our results from using frames of 64 samples are comparable with using 128 samples with slight improvements in the resolution of the beat-to-beat intervals coming from using the shorter frame.

The envelope signal was obtained using power spectral analysis and a threshold level to map the flow of a high velocity red blood cell in the vessel being insonated with ultrasound. The power in the signal varied throughout the recording due to adjustments of the transducer and maternal or fetal movements, which posed a problem in the selection of a suitable threshold level. An optimum threshold was chosen using the method of Evans *et al.* (1989) which worked well, but due to this variable signal level there were sections where points were not detected leading to gaps in the envelope signal. A threshold level using the mean of the spectrum and also an adaptive thresholding method with the point of reference being the maximum point in the power spectrum with different fractions of this value were used as the threshold but these methods introduced more noise into the resulting envelope signal.

It was possible to produce a clean envelope signal providing the signal to noise ratio was high but in measuring beat-to-beat intervals, problems occurred with resolution. As was seen in figure 6.7 the intervals fall into a number of frequency bins, which does not illustrate the variability of the length of the heart beats: the goal of this work. Overlapping the signal does improve results but the extent of overlapping required is not recommended since it is computationally intensive and the content of consecutive frames is very similar.

Amplitude demodulation does not have these problems associated with it and the correlation between the beat-to-beat intervals derived here using amplitude demodulation and frequency demodulation compared with the intervals found from the machine derived envelope signal is good. This amplitude demodulation however only works because the original Doppler audio signal is high pass filtered to eliminate wall thump noise. Referring to the Doppler shift equation, it is noted that the velocity of the scatterers of the ultrasound is proportional to Doppler shift therefore frequency demodulation is considered to be the preferred method of analysis. However the computational time needed to perform this more theoretically correct frequency demodulation is long, owing to the amount of signal overlap needed for high resolution and the shortness of the frames of data used, therefore the machine derived envelope signal will be used for the rest of this work.

6.9 Conclusions

It has been shown that an envelope signal can be obtained from the Doppler audio data and this shows promise particularly where there was noise in the signal as the low signal to noise ratio produced gaps in the envelope signal which could easily be detected as places where the signal to noise ratio was low.

It was possible to obtain reasonable beat-to-beat interval measurements using frequency demodulation by analysing short frames of data, at least 128 samples or even 64 samples and by overlapping by 93.75%. Amplitude demodulation also produced good results and both sets of results from frequency and amplitude

demodulation were comparable with the beat-to-beat intervals from the machine derived envelope signal.

7.0 Deriving heart rate variability from invasively and non-invasively obtained fetal heart rate signals

7.1 Introduction

The main difficulties associated with the current methods of detecting fetal distress have been covered in chapter 3. In this chapter the invasive and non-invasive methods of monitoring fetal heart rate for the study of heart rate variability will be compared. In the previous chapter, the Doppler ultrasound signal was looked at in detail, both the unprocessed audio signal and the processed envelope signal. In this chapter the machine-derived envelope signal will be used throughout.

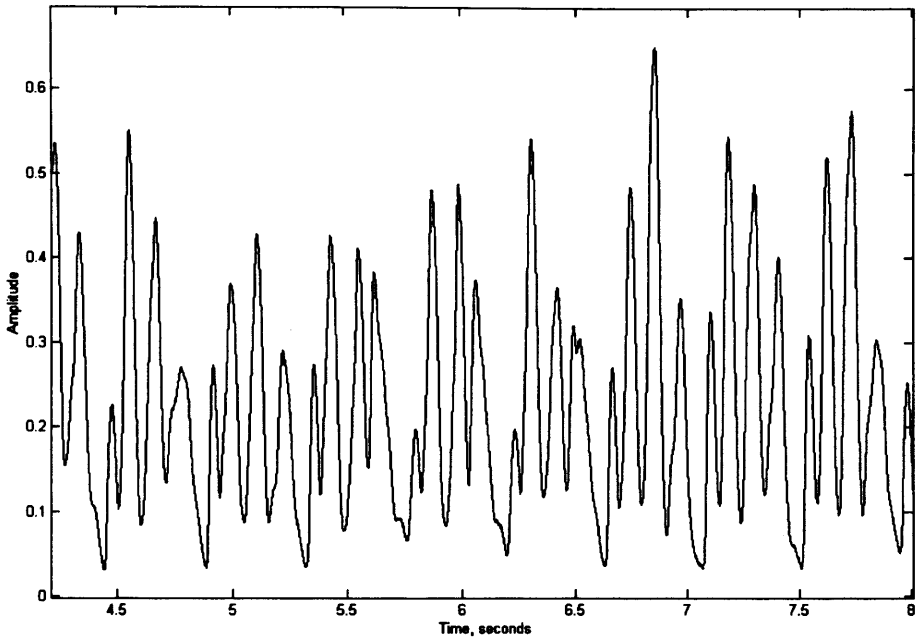
7.2 Autocorrelation

In the previous chapter it was noted that non-invasively obtained signals, from Doppler ultrasound can be very useful, however they can suffer greatly with problems of noise arising from fetal or maternal movements, muscle contractions, arterial blood flow and movement of the transducer.

The HP4080A machine uses autocorrelation, which is a method of signal processing. This was introduced to aid in fetal heart rate analysis in the early 1980s. The method works by multiplying the signal by a time delayed version of itself and in doing this any periodicities in the signal such as peaks in blood velocity, will be enhanced and noise which is not periodic, will decrease. The equation for the autocorrelation function is $R(\tau) = \frac{1}{N}\sum_{k=1}^{N} a(k.\Delta t).a(k.\Delta t - \tau)$ where the range of τ is 1.5 seconds (HP8040A users' manual).

The following figures show an example of a Doppler envelope signal before autocorrelation and after.

(a)



(b)

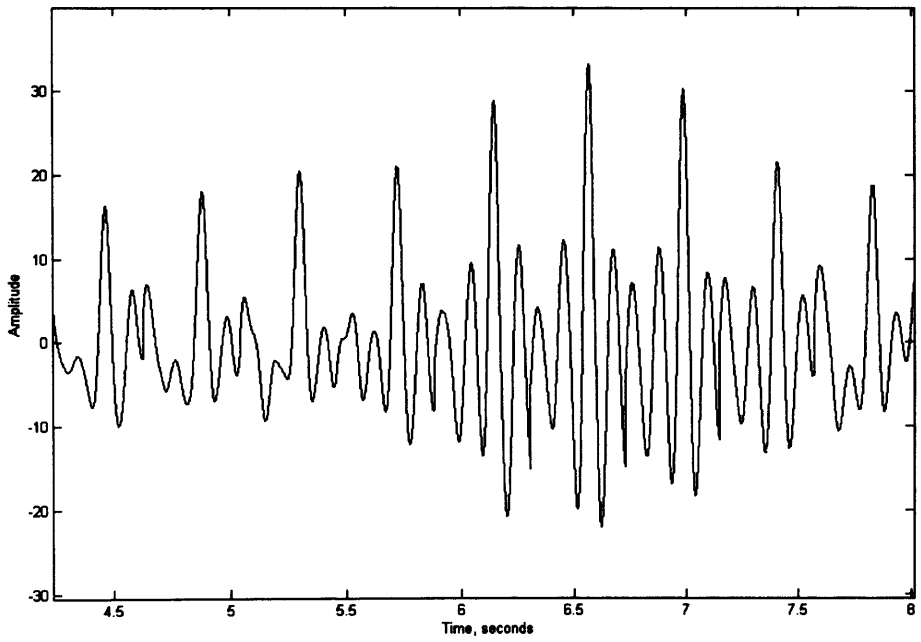


Figure 7.1: *An example of the improvement gained by using autocorrelation to help distinguish the peaks occurring in the signal. (a) original signal and (b) signal after autocorrelation.*

Divon *et al.* (1985) performed a study which tested electronic fetal heart rate monitors using autocorrelation with those which do not and found that when the signal to noise ratio was high, both machines provided a reasonable representation of heart rate. When signal to noise ratio was low the monitor which did not use autocorrelation failed to provide an output which could be interpreted. Boehm *et al.* (1986) in a similar study also verify these findings.

7.3 This study

Autocorrelation is very useful and has now become an accepted method for processing heart rate signals. However, it is still maintained that direct ECG monitoring from the scalp electrode sometimes referred to as the gold standard of heart rate monitoring, is more accurate and often caution is expressed in the analysis of Doppler ultrasound signals.

In this work intrapartum signals are looked at first and the beat-to-beat intervals found from the Doppler ultrasound signal are compared to those found from the ECG signal. The algorithm for finding heart rate variability, used to show the presence of asphyxia in rats in chapter 5, will be applied to this data. Signals acquired at antepartum will also be analysed in this way. This chapter focuses on the development and implementation of the algorithms and tests them off-line for some normal patients.

7.4 Data collection and methods of analysis

Fetal heart rate data was collected using a Hewlett Packard 8040A cardiotocograph machine. This machine produces a printed paper output of fetal heart rate, where each point is the average of three heart beats (Pearce and Steel 1987) and the strength of contractions, which is detected by a strain gauge attached to the mother's stomach (HP8040A users' manual). Numerical values for mean heart rate and mean contraction strength (toco) are also displayed digitally.

For the data acquisition a PCIMCIA analogue to digital converter card was used, connected to a laptop. An interface box connected the cable from the laptop to the HP8040A and it was possible to collect up to four signals from the Hewlett Packard machine. The four signals collected at any one time were the toco signal, the ECG signal from the scalp electrode and the blood flow signal in the form of Doppler envelope and Doppler audio signals. These four signals were collected for an hour each from four fetuses during the first stage of labour. The Doppler envelope signal was collected from six fetuses for a total of 12 hours 35 minutes, mainly during the first stage of labour. Three sets of antepartum data of up to 40 minutes each were collected from mothers at greater than 30 weeks gestation but not in labour. Permission to collect the data and analyse it for the purposes of this research was obtained from the mothers prior to collection. Following collection, off-line analysis was performed on the signal.

7.4.1 Data processing: ECG

The scalp ECG heart rate data was filtered using a low-pass filter with cutoff frequency 80 Hz. In all but one case this resulted in a clean signal with the R-points easily identifiable. One of the ECG records had parts of the signal missing (4thNov02) where the clip became detached from the fetus' head: these were removed from the record prior to processing.

The peaks were detected using a constant threshold and to avoid detecting the same beat twice, a refractory period, chosen to be a length of time short enough that another

beat could not physically occur (0.3s), was used. The distances between consecutive R-points were then found. This is shown in figure 7.2.

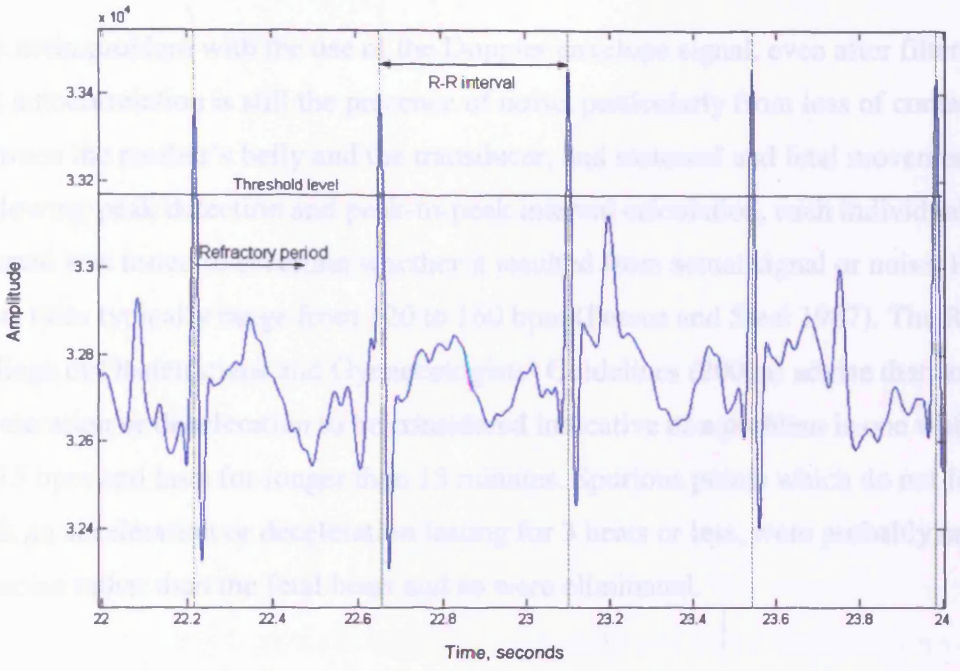


Figure 7.2: *This shows the thresholding method used for detecting the R-peaks of the ECG.*

7.4.2 Data processing: Doppler envelope

The Doppler envelope signal was more difficult to process due to the presence of noise arising from different sources. The signal was resampled to 1000Hz, filtered using a low-pass filter with cutoff frequency 30 Hz. Next, autocorrelation was used to help distinguish the blood velocity main peaks.

Unlike the ECG signal, the peaks in the blood velocity signal were of differing amplitude dependant on the signal strength, therefore an adaptive thresholding method was used. To begin detection, an arbitrary threshold was chosen, when a point exceeded this, the maximum point close to this first point was detected as the peak.

An average of the amplitude of the present peak and those of the two previous peaks was used to find the new threshold level. Again a refractory period was used to reduce the possibility of detecting the same beat twice.

The main problem with the use of the Doppler envelope signal, even after filtering and autocorrelation is still the presence of noise, particularly from loss of contact between the mother's belly and the transducer, and maternal and fetal movements. Following peak detection and peak-to-peak interval calculation, each individual interval was tested to ascertain whether it resulted from actual signal or noise. Fetal heart rates typically range from 120 to 160 bpm (Pearce and Steel 1987). The Royal College of Obstetricians and Gynaecologists' Guidelines (2001a) advise that an acceleration or deceleration to be considered indicative of a problem is one which is +/-15 bpm and lasts for longer than 15 minutes. Spurious points which do not form such an acceleration or deceleration lasting for 3 beats or less, were probably caused by noise rather than the fetal heart and so were eliminated.

7.4.3 Data processing: Heart rate variability analysis

For both sets of data cubic spline interpolation at a resample rate of 4Hz was used and then heart rate variability analysis was performed. Firstly, a quantitative measure of beat-to-beat variability was calculated, by finding the standard deviation of 30 second sections of data. Power spectral analysis using the autoregressive power spectrum with model order 16 was found; Poincaré plots showing very short-term variability and histograms of beat intervals showing long-term variability were looked at.

Collecting data from the scalp electrode during labour was difficult because this sort of monitoring is only undertaken in women classified as high-risk and even then it may not be possible to attach the clip, so non-invasive monitoring is used instead. In order that the midwife and clinician's normal practice was not interfered with, fetal scalp clips were not used solely for the benefit of this study; data was collected from those fetuses who were already being monitored in this way. High-risk women are also more likely to have a caesarean section which also prevented further data collection.

It was only possible to collect four sets of ECG and Doppler data together and so some solely obtained Doppler data is also presented further showing that measures of HRV data can be derived from non-invasively collected Doppler signals.

7.5 Results

7.5.1 Intrapartum: Comparison of intervals derived from ECG and Doppler ultrasound heart rate recordings

In performing the comparison of beat intervals for the ECG and Doppler data it is recognised that there will be small differences present, therefore an error margin of 5% of average heart rate was used. This comparison for the four sets of ECG and Doppler heart rate data obtained during labour is given in table 7.1; a plot of the intervals for the 22nd July 02 record is shown in figure 7.3. The corresponding plot of heart rate variability is given in figure 7.4. A comparison of histograms showing long term variability of lengths of beats from the ECG and Doppler ultrasound data for this same record are given in figures 7.5. In two of these four records problems in picking up the signal with the transducer occurred and so a large part of the signal had to be rejected as noise. For the 6thNov02 recording, there were also difficulties in attaching the scalp clip for the ECG recording.

Table 7.1: *Percentages of intervals derived from the ECG signal and Doppler ultrasound signal which were within a 5% error margin, the percentage of Doppler signal eliminated as being noise and percentage of outlying points obtained from the Doppler signal. The R-R intervals obtained from the ECG signal are considered to be the gold standard.*

	% within margin	*% outlying points*	*% noise*
22nd July 02	68.1	10.0	21.9
4th Nov 02	57.9	14.1	28.0
6th Nov 02	15.6	18.9	65.4
20th Nov 02(1)	34.9	2.0	63.1

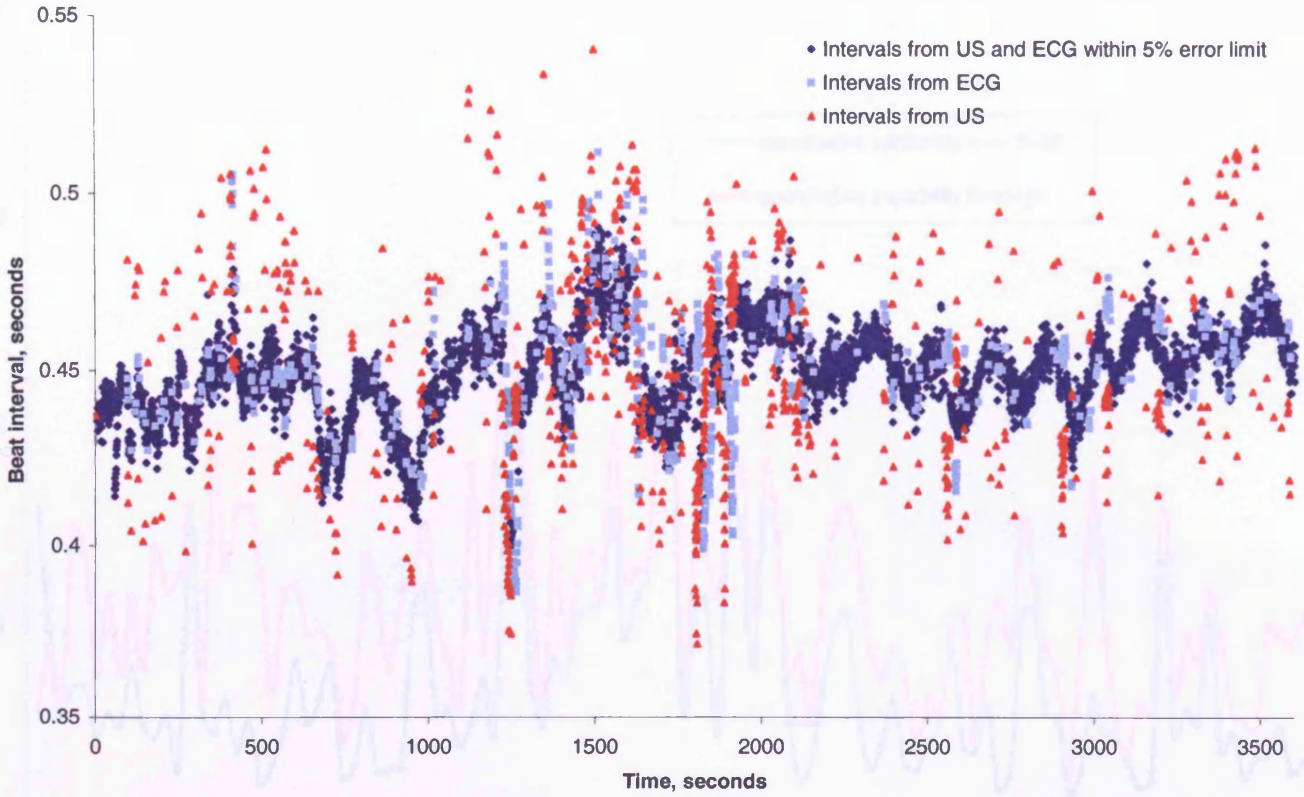


Figure 7.3: *A plot of beat-to-beat intervals derived from ECG and Doppler ultrasound data which are within a 5% boundary (dark blue). The outlying intervals from the ECG signal (light blue) and outlying intervals from the Doppler ultrasound data (red) are also shown.*

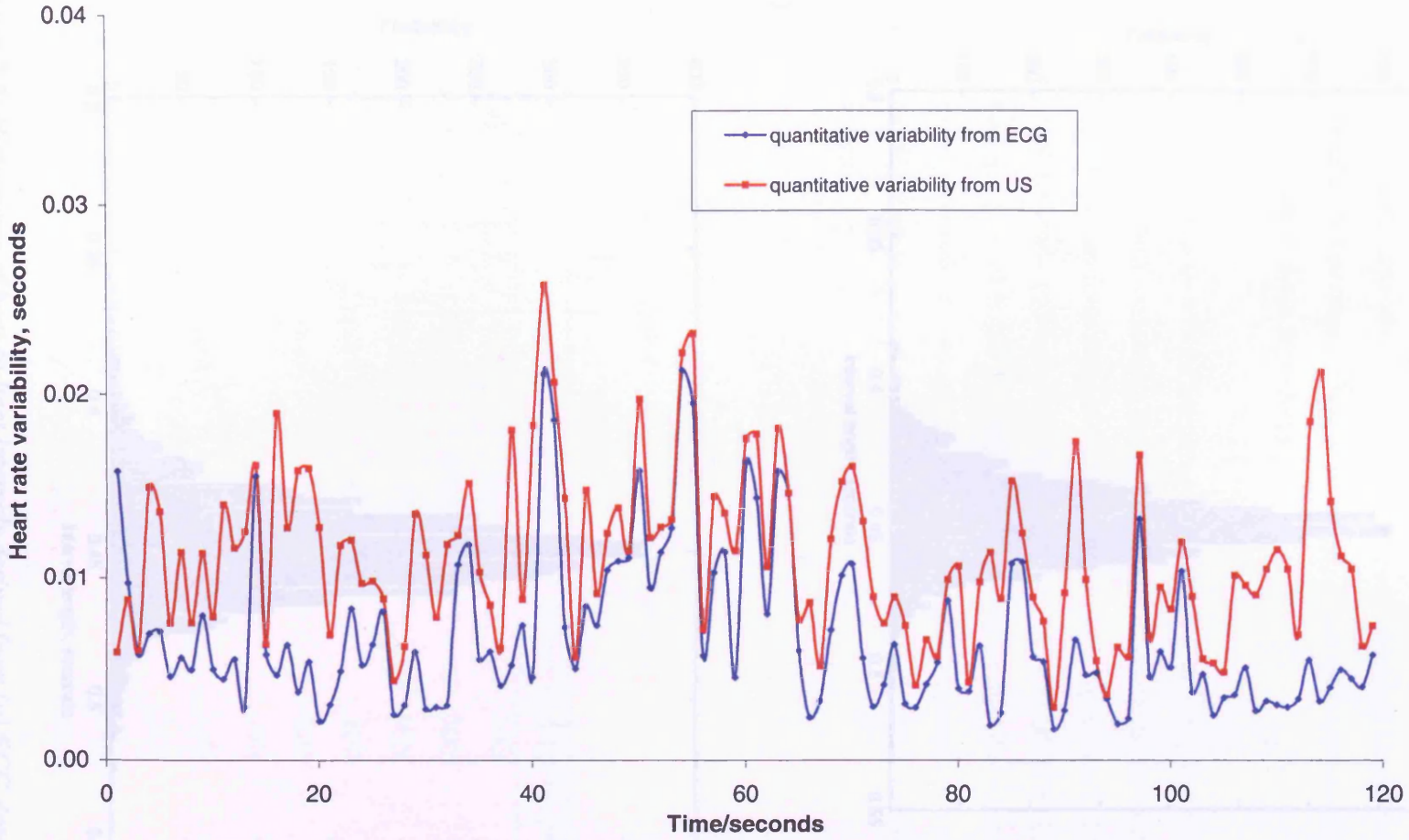
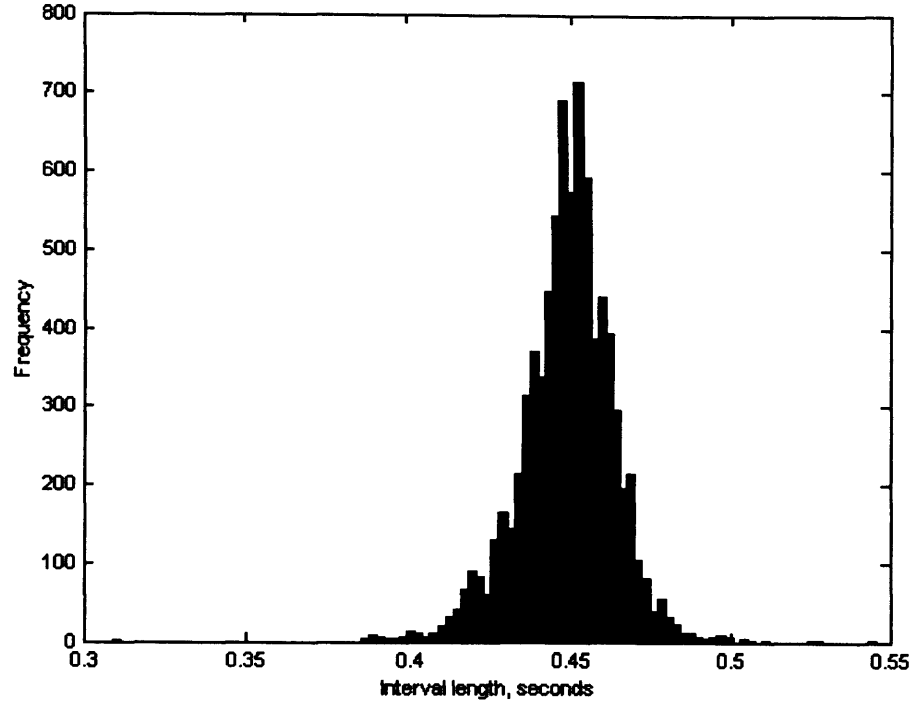


Figure 7.4: *A plot showing heart rate variability calculated from the beat-to-beat intervals derived from the ECG and Doppler ultrasound signals.*

(a)



(b)

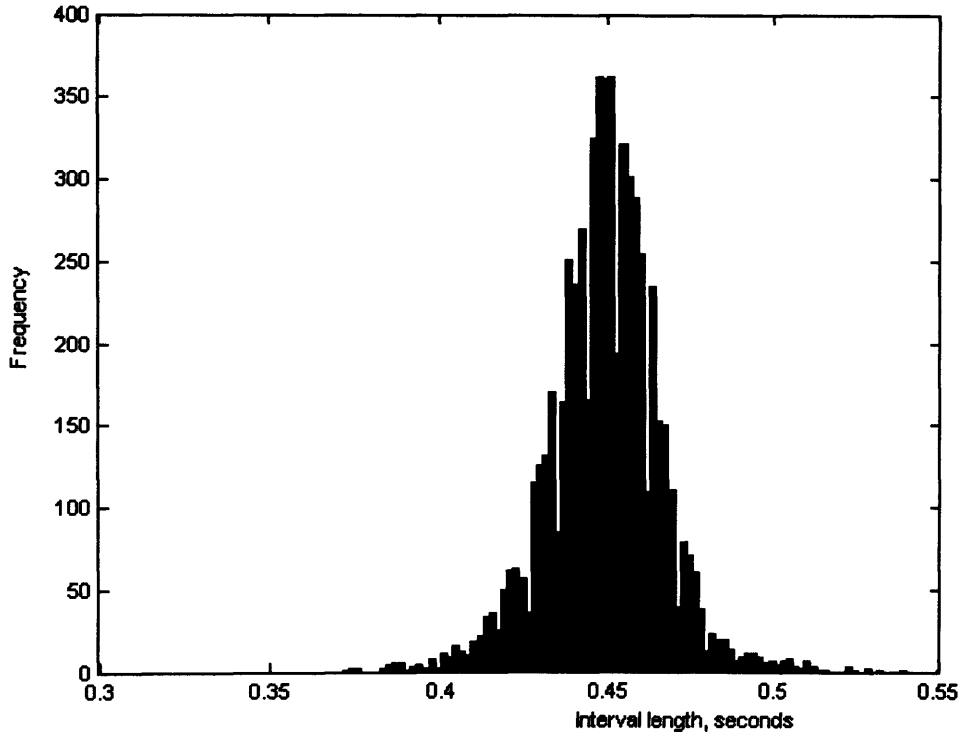


Figure 7.5: *Histograms of beat-to-beat intervals derived from (a) ECG data and (b) ultrasound data.*

7.5.2 Intrapartum: Results obtained from solely collected Doppler ultrasound heart rate data

Table 7.2 shows the records which were collected containing just Doppler data and the percentage of signal present in these recordings. There were similar, high levels of noise present in some of these recordings.

It was possible to record data from one fetus up until birth, showing that the collection of this data for analysis of variability throughout labour is viable however the signal loss due to the increasing frequency of contractions as birth approached, increased. The beat-to-beat intervals and a plot of the quantitative measure of HRV for this set of data are shown in figures 7.6 and 7.7. When a contraction occurs, the blood supply to the fetus may be momentarily reduced or cut off causing a deceleration in heart rate. These two factors contribute to the slight increase in heart rate variability towards the end of the record.

Table 7.2: *Table of records showing amount of signal present in heart rate signals collected during labour using just non-invasive monitoring.*

	Duration	% signal	Sampling frequency/Hz
15th May 02B	2 hours	43.6	300
20th May 02A	1 hour	60.9	300
20th May 02B	1 hour	58.1	300
22nd May 02A	2 hours	66.0	300
22nd May 02B	2 hours	42.3	300
22nd May 02C	1 hour	22.4	300
29th May 02A	17 mins	63.5	1000
29th May 02B	108 mins	59.5	1000
19th Jun 02	30 mins	76.0	2000
20th Nov 02(3)	1 hour	74.7	2000

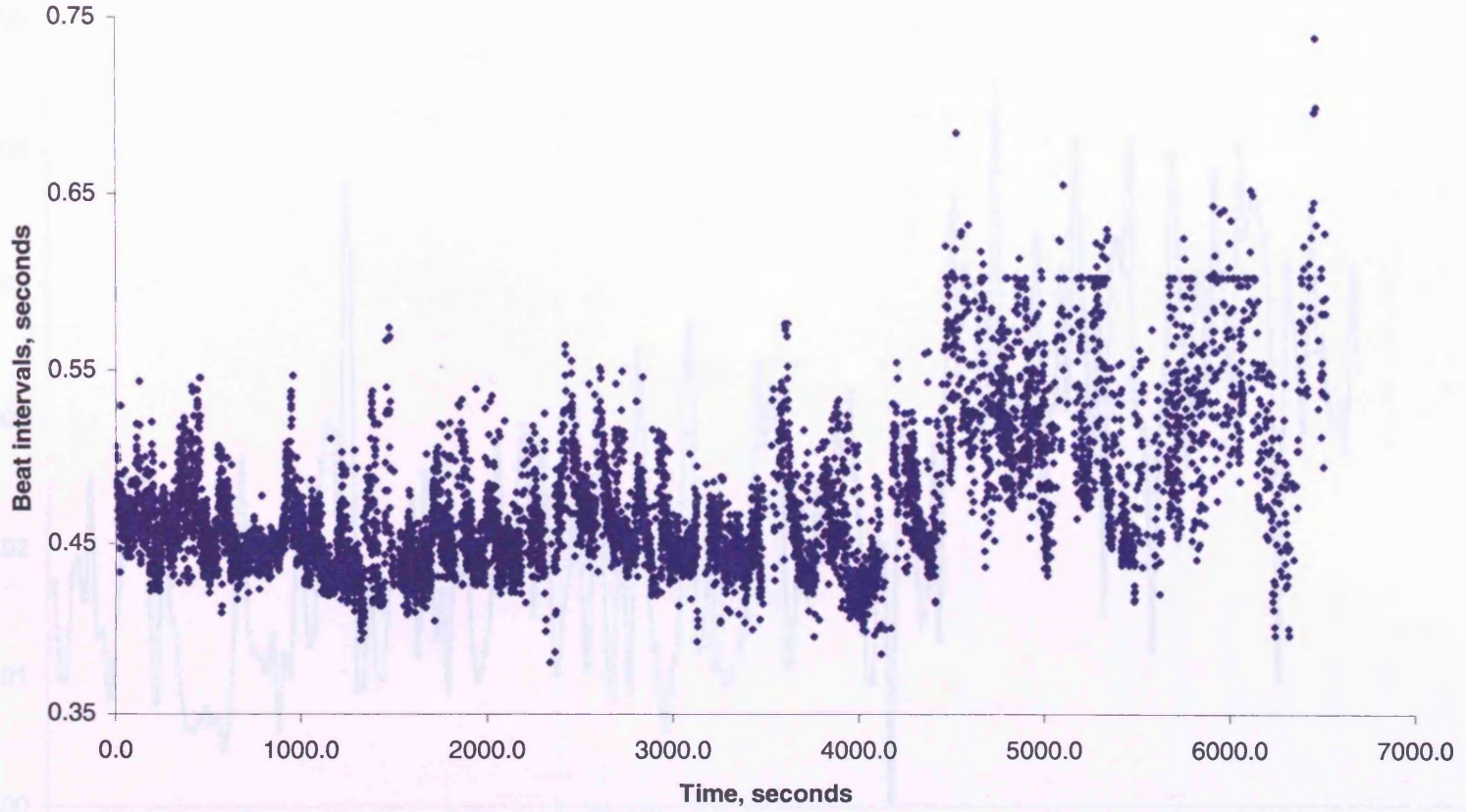


Figure 7.6: *Plot of beat-to-beat intervals from a fetus; birth occurred at the end of this record.*

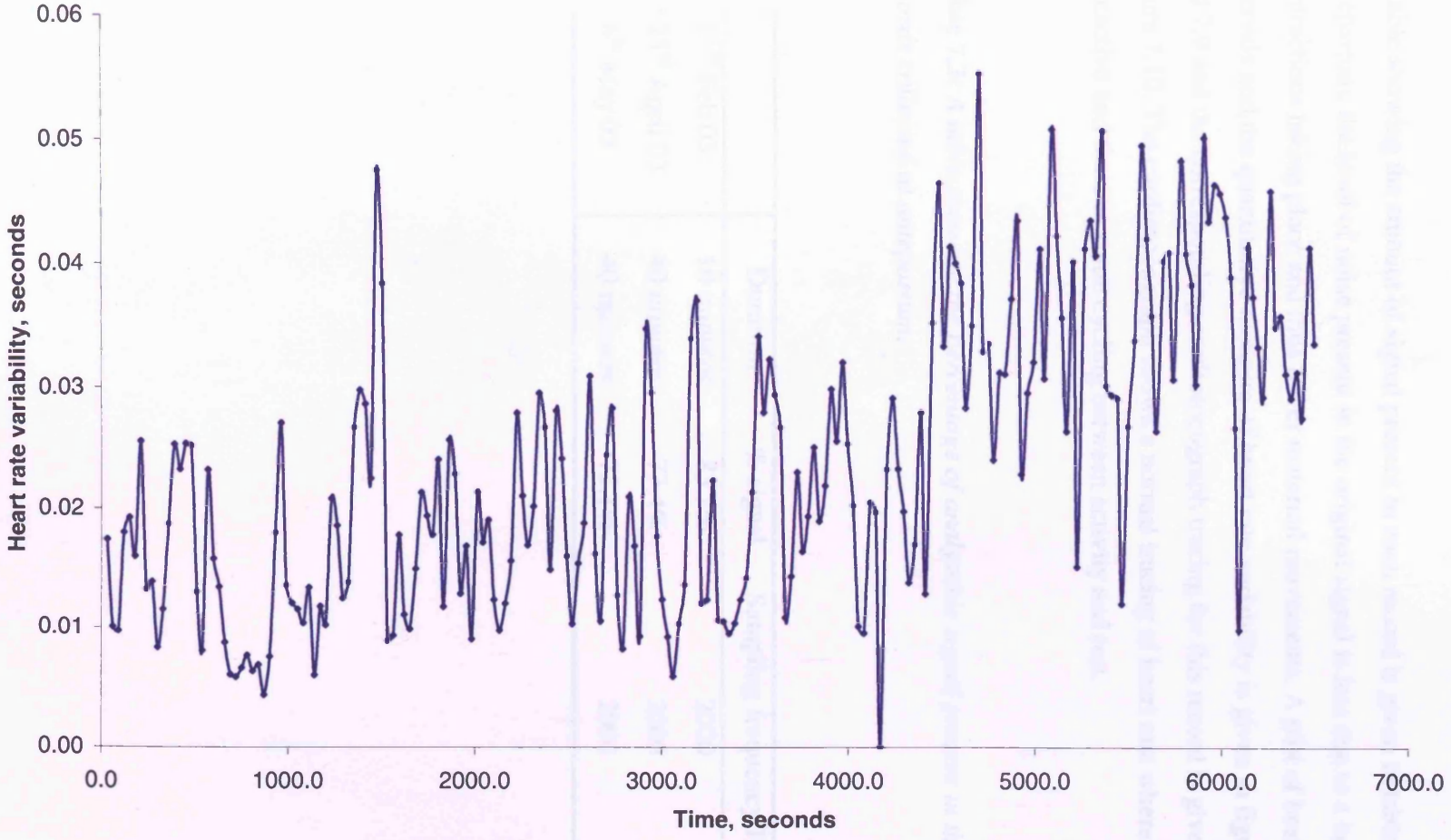


Figure 7.7: *Plot of HRV calculated from beat-to-beat intervals from a fetus monitored until birth*

7.5.3 Antepartum: Results obtained from Doppler ultrasound fetal heart rate collected before labour

A table showing the amount of signal present in each record is given in table 7.3: at antepartum, the level of noise present in the original signal is less due to a lack of contractions taking place and thus fewer maternal movements. A plot of beat-to-beat intervals and the quantitative measure of heart rate variability is given in figures 7.8 and 7.9 and the corresponding cardiotocograph tracing for this record is given in figure 7.10. The cardiotocograph shows a normal tracing of heart rate where the fetus is reactive and there is some cycling between activity and rest.

Table 7.3: *A table showing the percentage of analysable signal present in those records collected at antepartum.*

	Duration	% signal	Sampling frequency/Hz
11th Feb 03	10 minutes	83.7%	2000
23rd April 03	40 minutes	73.4%	2000
6th May 03	40 minutes	72.1%	2000

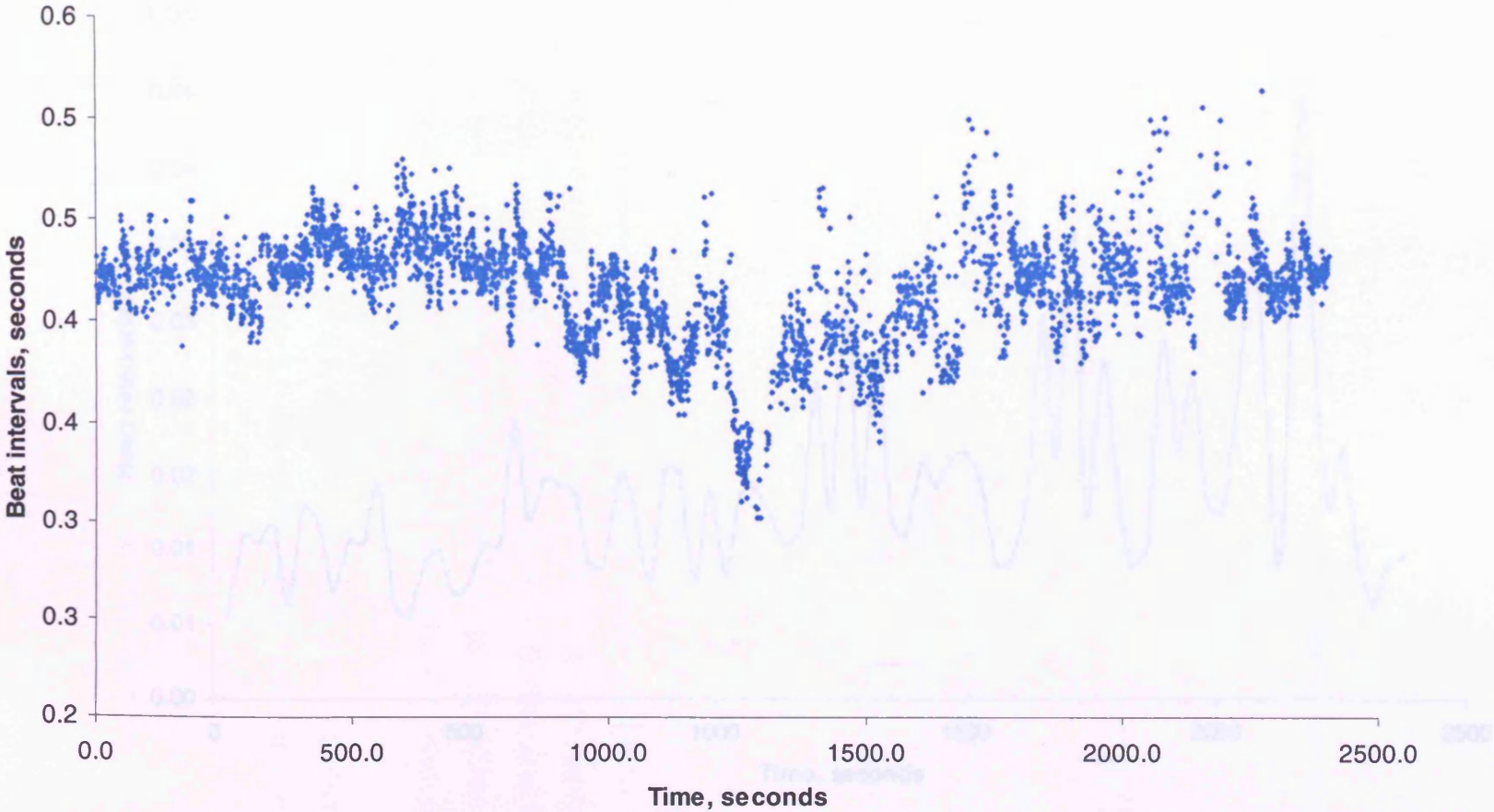


Figure 7.8: *Beat-to-beat intervals found from antepartum data taken from the Doppler ultrasound transducer.*

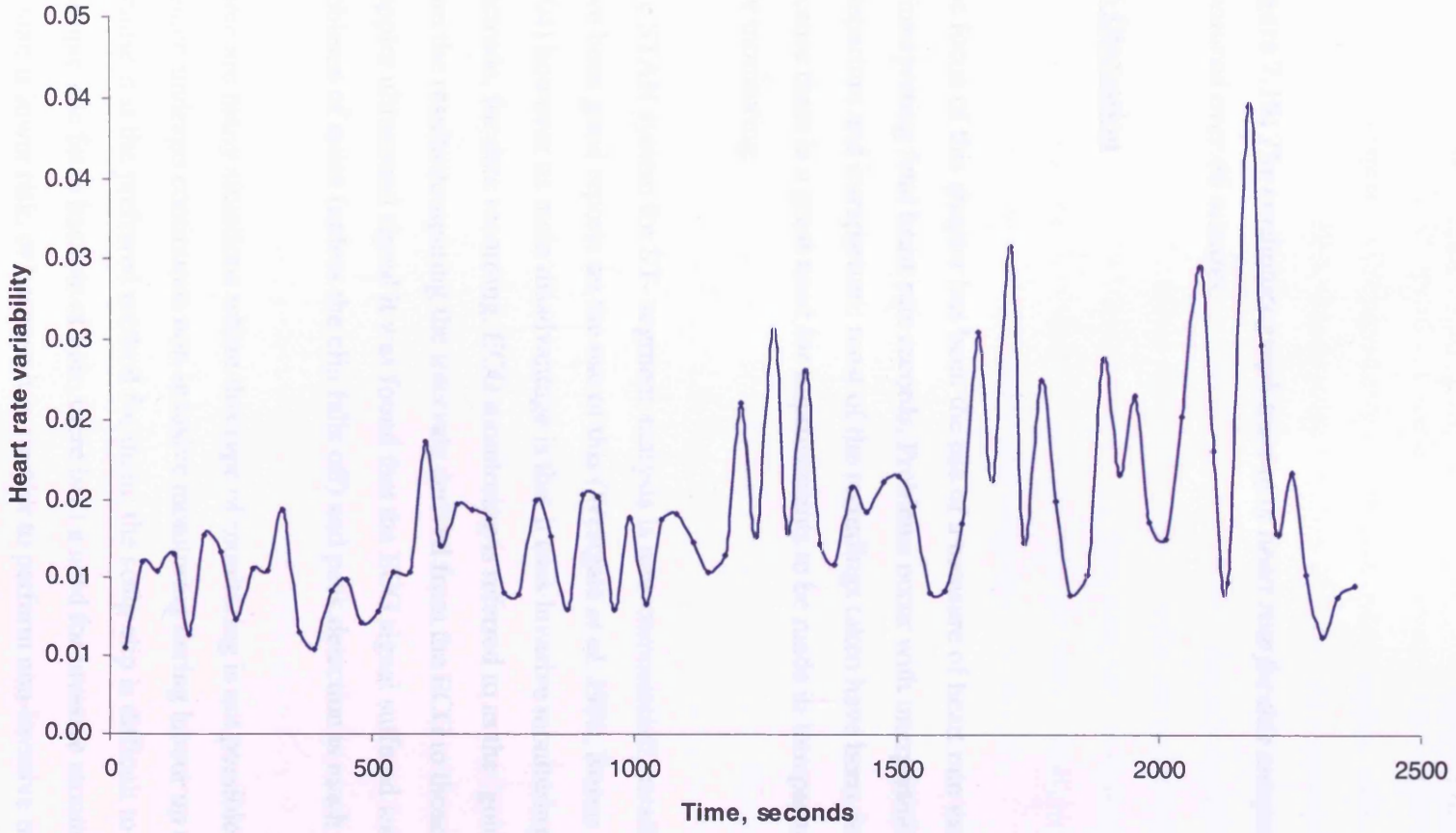


Figure 7.9: *Plot showing the quantitative measure of heart rate variability for an antepartum record.*

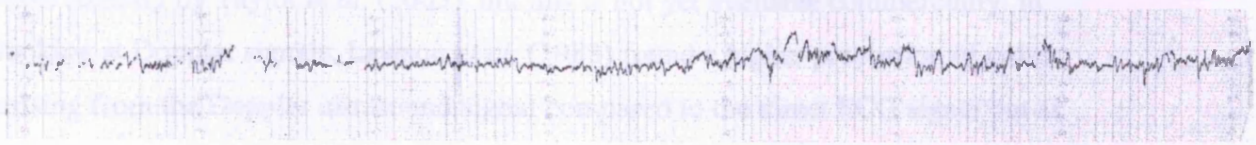


Figure 7.10: *The cardiotocograph tracing of heart rate for this antepartum record, measured over 40 minutes.*

7.6 Discussion

The focus of this chapter has been the use of a measure of heart rate variability to aid in interpreting fetal heart rate records. Problems occur with interpretation at both antepartum and intrapartum: most of the recordings taken have been during labour, because there is a great need for improvements to be made in intrapartum fetal heart rate monitoring.

The STAN system for ST- segment analysis is now commercially available and there have been good reports on the use of this (Westgate *et al.* 1992, Rosen and Luzietti 1994) however its main disadvantage is that it uses invasive monitoring, the scalp electrode, for data recording. ECG monitoring is referred to as the 'gold standard' and from the results comparing the intervals derived from the ECG to those from the Doppler ultrasound signal it was found that the ECG signal suffered less from problems of noise (unless the clip falls off) and peak detection is much easier.

There are many situations where this type of monitoring is not possible or ideal: many women undergo continuous non-invasive monitoring during labour up until birth because it is the preferred method for them: the scalp clip is difficult to attach if for example, the fetus has lots of hair; there isn't a need for invasive monitoring if the woman is lower risk, or because it is simpler to perform non-invasive monitoring.

The only method currently in use for non-invasive monitoring is the Doppler ultrasound transducer. There have been efforts to obtain fetal ECG non-invasively,

most recently by Taylor *et al.* (2003), but this is not yet available commercially. In looking at Doppler signals, Lawson *et al.* (1983) found a higher proportion of noise arising from the Doppler ultrasound signal compared to the direct ECG signal but as Fukushima et al. (1985) point out, the ECG signal arises from the electrical activity of the fetal heart whereas the signal from the ultrasound transducer arises from the mechanical activity of the heart which explains why it is to be expected that the Doppler signal has a higher noise content. Similarly here, the noise content in some Doppler records was high but following elimination of this, the overall results from the comparison of the intervals derived from the Doppler ultrasound to those derived from the ECG were good. It was found in the best case, that fewer than 10% of points lay outside a 5% error boundary, which shows the potential of using non-invasive Doppler heart rate data particularly if clean signals are collected.

Numerous studies since the introduction of electronic fetal heart rate monitoring in the 1960s have demonstrated the need for better interpretation of fetal heart rate traces (Lotering *et al.* 1982, Borgatta *et al.* 1988, Oppenheimer and Lewinsky 1994, Zimmer *et al.* 1998, Berkus *et al.* 1999, Huddleston 1999, Sweha *et al.*1999, Parer and King 2000), using a method which is universally applicable, to overcome inter-observer variations. Westgate *et al.* (1999) note the importance of fetal heart rate variation in its fluctuations around the baseline rate as an 'essential element of intrapartum fetal heart rate interpretation' and work has been undertaken in quantifying this as an actual measure in beats per minute but no such attempt has been successful in predicting distress during labour so far (Parer *et al.* 1985, Samueloff *et al.* 1994).

Here a different measure of variability has been proposed: a numerical measure calculated over 30 second sections of beat-to-beat intervals derived from either ECG or Doppler ultrasound data. This is different to measures already mentioned (Parer *et al.* 1985, Samueloff *et al.* 1994) and in fact to the clinical measure of heart rate variability also, as it does not refer variability to a baseline rate. In all cases, normal labours were monitored and as expected, a relatively constant measure of variability was found. A reasonable comparison of this measure for the ECG and Doppler data was achieved: the variability for the Doppler results was slightly higher (fig 7.4) but followed the same pattern as that for the ECG results. These are positive results: it has been shown that data can be acquired and a measure of variability calculated for

invasively and non-invasively obtained signals. The fact that they are comparable is an important result since non-invasive monitoring is used so frequently, but thought inferior to invasive monitoring.

When considering the application of this work, lessons can be learnt from Pardey *et al.* (2002) who summarise the progress made on a commercially available computerised fetal heart rate monitor for use at antepartum: the Sonicaid system. This system is promoted as an aid to clinical judgement not a replacement for, which is very important to note when considering the algorithm: it is not feasible to attempt to or to want to replace the CTG due to its wide application in this field, rather to help interpret the information it produces in a way which may be helpful to the clinician and present this alongside the usual recording.

Although the original aim was to just look at intrapartum data it was found that antepartum data could be acquired and analysed and this suffers from fewer noise problems. It is useful to compare the Sonicaid system with this algorithm: Sonicaid gives a measure of short-term variability which cannot be seen by eye but otherwise performs the same analysis that would be performed visually by the clinician. The recording can be 10 minutes for a healthy reactive fetus or up to an hour for a fetus who is non-reactive or may have a problem and in this case, an overall verdict may not be given (Pardey *et al.* 2002). At antepartum the issue of timing would not appear to be so crucial however it has been reported in one case that the one hour Sonicaid recording was undertaken and following an inconclusive outcome the baby was delivered: it was thought that an earlier delivery could have been beneficial (Gibb 2003). The issue of having a machine available for automated analysis of fetal heart rate is not clear-cut although there are advantages; a disadvantage to this type of antepartum monitor is the time required for the recording. The quantitative measure of heart rate variability calculated at real-time may provide an improvement to this and should be investigated further.

7.7 Conclusions

Noise existed in the Doppler recording to varying degrees and is the main problem in performing this type of analysis, however the wide applicability of non-invasive

monitoring demands that this should be persevered with. Improvements that could be made to actual signal collection include, aiming the transducer beam at a main fetal artery rather than the heart when attaching the transducer; the introduction of non-invasive ECG monitoring may also prove useful.

Despite the presence of noise, it has been shown that fetal heart rate signals collected invasively and non-invasively, are comparable following noise elimination and can be used in calculating a quantitative measure of heart rate variability. In all cases, this measure stayed at a constant level which indicated a fetus without problems.

The ability to collect data and calculate a measure of heart rate variability for intrapartum and antepartum monitoring has been demonstrated. Further work needs to be done in collecting more signals before the potential of this method can be fully realised.

8.0 Conclusions: The feasibility of using heart rate variability to detect distress

Asphyxial distress does not occur spontaneously: there must be a cause. In the fetus, throughout pregnancy and labour, there is a chance that due to an insufficient placental supply, asphyxia may occur. In such a circumstance the insult could be severe and long lasting or mild and repetitive. There could be serious damage or the fetus could have enough reserve to overcome the problem. It is not possible to know in individual cases, exactly what will happen although predictions can be made. This study has been undertaken to determine whether a measure of heart rate variability can be used to detect distress and if this will be useful in detecting fetal compromise.

Heart rate variability has been studied extensively since Sayers' work was published, which looked at the three main frequency components present in heart rate fluctuations (Sayers 1973). Following on from this there have been a number of studies, for example, looking into prognosis following myocardial infarction and diabetic neuropathy. The interest in heart rate variability analysis stems from the idea of using heart rate to make inferences about the health of the autonomic nervous system since it is this which regulates the beat intervals, so, by looking at the beat intervals, information about the nervous system can be found. Non-invasively obtained measures have very obvious advantages over invasive measures and are particularly useful when they are obtained continuously: these are good reasons for a study into another possible application of heart rate variability.

8.1 Is it feasible to use heart rate variability to detect distress?

Distress caused by asphyxia decreases heart rate which in itself is an indicator of a problem and is one of the main methods of detecting fetal compromise.

Using the standard deviation of 30 second frames of heart rate data as a measure of heart rate variability, produced a much more sensitive indicator of the occurrence of asphyxia when tested on heart rate data obtained from rats subjected to different periods of asphyxia. Although heart rate did decrease when asphyxia occurred, for

short durations of asphyxia, this measure of heart rate variability was far more sensitive than just looking at the average heart rate and the pH levels in the blood. In the delivery room, changes in average fetal heart rate and pH are of questionable use in identifying some cases of fetal distress and for fetal heart rate, problems can occur when deciding what constitutes a normal deceleration and what is abnormal. This measure of heart rate variability showed a dramatic change at the onset of asphyxia regardless of the length of the injury.

Frequency domain analysis of the heart rate variability data shows a different sort of response to the occurrence of asphyxia: the power in the spectra increases, its distribution changes and the respiratory sinus arrhythmia peak disappears. It is here that the work in looking at the optimum order of autoregressive processes is useful: short segments of data are necessary to allow these changes to be seen as they occur. It has been shown that it is feasible to use heart rate variability to detect distress.

8.2 Is it feasible to use heart rate variability to detect fetal distress?

Heart rate signals can be obtained from the fetus using the non-invasive Doppler ultrasound transducer and the invasive fetal scalp electrode; here a good comparison of beat-to-beat intervals and heart rate variability measure was obtained providing the noise level in the signal was low. The derivation of the Doppler envelope signal from the Doppler audio signal was looked at, using frequency demodulation and amplitude demodulation and both methods produced similar results but noise still existed in the signal. These problems with noise could be avoided if the placement of the Doppler transducer was altered so that the ultrasound beam is aimed at an artery rather than the fetal heart.

In all the normal labours monitored so far, the results have been as expected: there have been mild fluctuations in the measure of heart rate variability but no great changes in level have occurred.

It is not possible to know at this stage whether this measure of heart rate variability would be able to detect fetal distress to a high enough level of sensitivity to be

clinically useful: much more data will need to be collected before this discussion can be started, however it has been shown that it is feasible to collect the data necessary and to perform this analysis.

8.3 The context of this work

The clinical setting is very much different from that of the engineering laboratory: studies cannot be re-run to check results or restarted with alternative parameters, interesting cases have to be waited for and often then labour is replaced with Caesarean section. It is difficult to know following an intervention whether this was worthwhile or not. The inherent imprecision of this sort of work should also be acknowledged: all fetuses are different and will behave differently in responding to the stresses of labour.

However the possible benefits of such a technology being able to actually identify, rather than suspect fetal distress are huge: more informed decisions on intervention as necessary, during and before labour; the ability to distinguish between those fetuses who need to be delivered quickly and those who do not, could reduce fetal illness or death, Caesarean section rates, medical costs and midwives' time; the ability to know how long the injury lasted and whether it was continuous or intermittent would aid in deciding treatment.

It was never the intention that this algorithm should replace the experienced clinician, rather to give an extra form of analysis to aid in decision making. For such a technique to be accepted into clinical practice, there is still a long way to go. However from the literature and speaking to clinicians it is obvious that such a system would be welcomed on the delivery suite, so should be studied further.

8.4 Future work

The main recommendation for this work is that more data needs to be collected in order to validate the results already achieved. The system is intended to identify fetuses suffering from distress, therefore it is essential that records are collected from abnormal cases where it is suspected that distress is occurring and a retrospective analysis carried out on the capacity of the system to identify the occurrence of a problem. Cases where it is often difficult to identify distress include high-risk fetuses such as those suffering from intrauterine growth retardation and it would be useful to carry out work in these situations.

Further work could be also done with regard to the elimination of noise from the Doppler recording which would allow the beats to be recognised more easily. For example, Vali (2003) used a different technique for elimination of erroneous data points and achieved a slightly better comparison of heart rate variability from ECG and the Doppler envelope for the record shown in figure 8.1. This should be explored further.

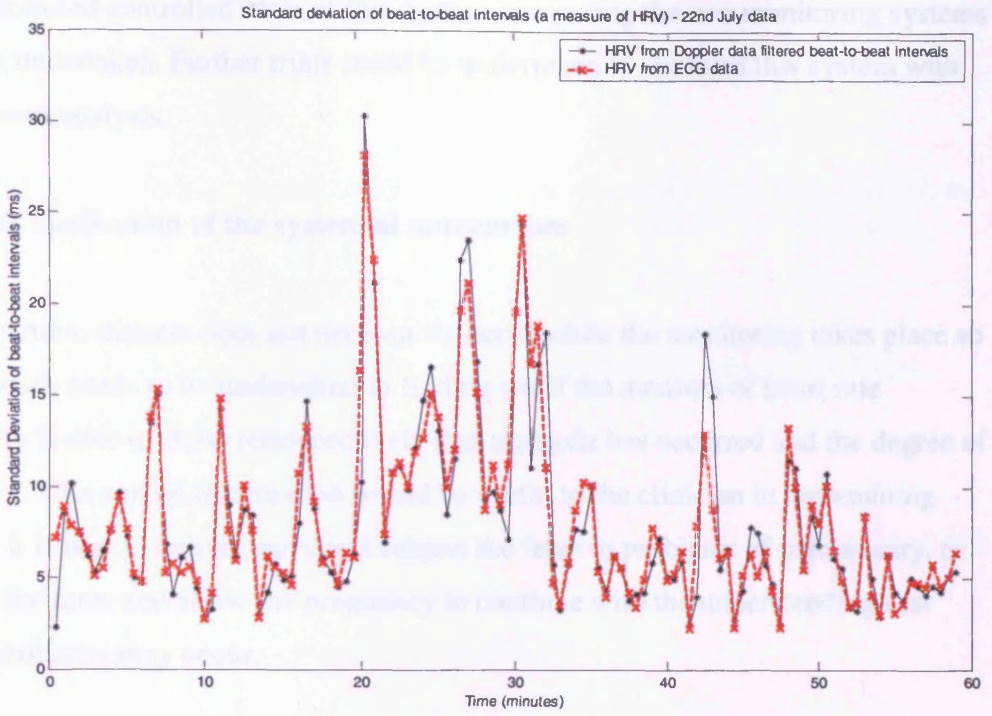


Figure 8.1: *Comparison of HRV obtained from ECG and Doppler envelope data where a filtering method was used to eliminate erroneous points.*

8.4.1 Trials where fetal asphyxia is known

It is essential to know if this method of heart rate variability analysis does identify fetal asphyxia in the same way that it has been show to identify adult asphyxia in the animal model. Many trials have been undertaken using the fetal lamb and it would be useful to be able to test our algorithm for differing lengths of asphyxia in the fetal animal model. This would be helpful in a number of ways: it would be possible to test the sensitivity of the measure for varying lengths of asphyxia; it would be interesting to look at the response of the fetus to short lengths of asphyxia to see if fetal reserve is great enough to overcome mild injuries; it would be useful to look at intermittent injuries to see if these are discriminated by the measure of heart rate variability.

8.4.2 Real-time analysis

The next step is to implement the heart rate variability analysis in real-time. It is intended that this algorithm should be used along side the cardiotocograph recording

and randomised controlled trials of this system comparing the two monitoring systems could be undertaken. Further trials could be undertaken to compare this system with ST-segment analysis.

8.4.3 The application of the system at antepartum

At antepartum, distress does not necessarily occur while the monitoring takes place so further work needs to be undertaken in finding out if the measure of heart rate variability is able to show retrospectively that asphyxia has occurred and the degree of the injury. This sort of information would be useful to the clinician in determining whether it is best to deliver early and subject the fetus to problems of prematurity, or to leave the fetus and allow the pregnancy to continue with the understanding that further problems may occur.

8.4.4 Conclusions

The two applications of this work are monitoring fetal well-being prior to and during labour. The next step for this project is the acquisition of more signals both at antepartum and intrapartum and then further consideration regarding the usefulness of the research should be undertaken.

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