ACIDOSIS AT BIRTH IN TERM INFANTS AND EARLY NEUROPHYSIOLOGICAL AND CARDIOVASCULAR CHANGES

ADRIENNE MARY FORAN
MB BCh BAO BA MRCPI (PAEDS)

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Department of Neonatology,

The National Maternity Hospital

Dublin 2

CONTENTS

DECLARATIONS

1. Submission

This thesis has not been submitted previously for a degree at this or any other university.

2. Statement of Originality

All the ideas contained and all the experimental work described in this thesis have been developed and performed by the author except where stated in the acknowledgements section.

3. Consent

Full and informed consent was obtained from all parents or legal guardians of the infant subjects involved in this study.

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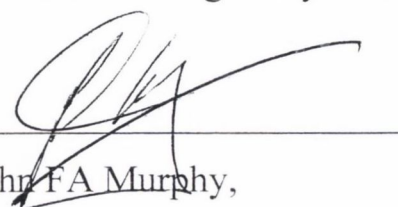
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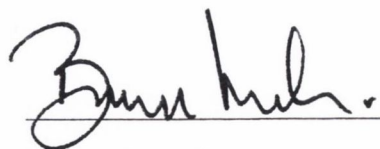
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5. Verification

As advisors of the work contained in this thesis we certify that the statement of originality is accurate.

John FA Murphy,
Consultant Neonatologist,
The National Maternity
Hospital,
Dublin 2.

Brian Lynch
Consultant Neurologist
The Children's
University Hospital
Dublin 1.

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ABREVIATIONS

A1 & A2	Ear Electrodes
AS	Active Sleep
ATP	Adenosine Tri-Phosphate
AW	Awake
AV	Atrio-Ventricular
BD	Base Deficit
BDECF	Base Deficit Extra-Cellular Fluid
BE	Base Excess
bpm	beats per minute
C	Central
CFM	Cerebral Function Monitoring
CK	Creatinine Kinase
CT	Computerised Tomography
CTG	Cardiotocography
CUSS	Cranial Ultrasound
ECF	Extra Cellular Fluid
ECG	Electrocardiogram
ECI	Electro-Cerebral Inactivity
ECS	Electro-Cerebral Silence
EEG	Electroencephalogram
EFM	Electronic Foetal Monitoring
EMG	Electromyography
EOG	Eye Movement Electrodes
F	Frontal Lobe
FECG	Foetal Electrocardiogram
FHR	Foetal Heart Rate
Fp	Fronto-parietal
FsPO$_2$	Oxygen saturation Foetal scalp
FTA	Failure to Advance

FTT	Fast Fourier Transformation
H^+	Hydrogen Ion Concentration
H_2CO_3	Carbonic Acid
HCO_3^-	Bicarbonate Ion Concentration
HF	High Frequency
HRV	Heart Rate Variability
Hz	Hertz
IBI	Inter-Burst Interval
kPa	Kilopascals
LF	Low Frequency
MRI	Magnetic Resonance Imaging
BE	Base Excess
NN	Normal to Normal
NE	Neonatal Encephalopathy
O	Occipital Lobe
P	Parietal Lobe
PCO_2	Partial Pressure Carbon Dioxide
PO_2	Partial Pressure Oxygen
PSD	Power Spectral Density
QS	Quiet Sleep
SA	Sino-Atrial
SaO_2	Oxygen Saturation
Secs	Seconds
SIDS	Sudden Infant Death Syndrome
SDNN	Standard Deviation of Normal to Normal Interval
T	Temporal Lobe
μV	Micro Volts
ULF	Ultra Low Frequency
VLF	Very Low Frequency

PUBLICATIONS AND PRESENTATIONS
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The effect of hypoxia and acidosis on the neonatal myocardium.

Foran A, Murphy T, Murphy J.

The Irish Perinatal Society, Annual Meeting, April 2004.

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Manometry measurements of the suck integrity in term infants with low cord pH and/or neonatal encephalopathy.

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The National Maternity Hospital, Holles Street, Dublin 2.

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Higher amplitude and frequency of bursts during quite sleep of the EEG are associated with a low cord pH at birth.

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The National Maternity Hospital, Holles Street, Dublin 2.

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Foran A.*, Lynch B#., Murphy J*.

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Clinical application and interpretation of the neonatal EEG.

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Guest Lecturer: Professor Joe Volpe, The Children's Hospital, Boston.

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SUMMARY

This thesis was mounted to evaluate and quantify the role of umbilical cord pH measurements in relation to the baby's clinical condition, electroencephalographic pattern, heart rate variability and analysis of sucking activity as measured by manometry.

The first limb of my research related to the application of 30 lead digital EEG recordings of term newborn infants with cord pH values≤ 7.25. In the early (48 hours) post-natal period EEG changes were identified during quiet sleep (QS). The nature of these changes was in relation to the maximum amplitude, frequency, number of sharp waves and length of the interburst interval (IBI). These were all increased in the more severely acidotic babies (cord pH ≤ 7.0), regardless of their clinical status. Using digital EEG technology I was able to identify the emergence of a spectrum between sub-clinical and clinical encephalopathy.

My results also offer reassurance in the frequently encountered clinical scenario of a clinically well infant who is mildly to moderately acidotic (i.e. pH 7.01-7.25) as all these infants had normal EEG recordings.

My findings concentrate on those who are severely acidotic (i.e. pH $\leq$ 7.0). This target group have a much higher rate of clinical encephalopathy and do appear to have sub-clinical changes manifest on their EEG recordings even when appear clinically normal. We cannot accept this subgroup of infants as normal, so measures to avoid severe acidosis developing in the perinatal period need to be put in place. Further

investigation to identify those infants at risk of dropping their pH to below 7.0 is required and it is paramount to address a pH ≤ 7.0.

The second limb of my thesis related to acidosis at birth and manometric suck patterns. Suck has always been regarded as a useful clinical tool in assessing term infants with neonatal encephalopathy (NE). I devised the sucking apparatus to analyse and quantify the frequency and pressure of the infant's suck. Three patterns clearly emerged. Firstly the clinically normal infants had an average frequency of strokes of 115 over a five minute epoch, the majority of these (70) were in the highest pressure band of −20 to −30 mmHg and their intersuuck interval was on average 14 seconds. Secondly those with definite encephalopathy had a much lower overall frequency of strokes (75) with less than half (30) being in the highest-pressure band and a much more prolonged intersuck interval of 40 seconds. Thirdly this technology also highlighted differences in the sub-clinical group. Those infants with a pH ≤ 7.0 but who appeared clinically

normal had differences in their sucking patterns compared to the clinically normal infants with pH values of 7.01-7.25. Firstly their overall frequency of strokes was lower (76.2 Vs 115) and secondly their number of strokes in the higher-pressure band was lower (49 Vs 70); however the length of their inter-suck interval was the same i.e. 14 seconds.

This technology was able to identify babies who had sub-clinical changes in their sucking pattern. More subtle aspects of changes in babies suck in relation to low cord pH also emerged. These findings suggest that this could prove a very useful bedside tool in evaluating babies suck response and how it changes with increasing maturity and in the presence of neurological compromise.

The third limb of my research examined the relationship between acidosis at birth and heart rate variability (HRV). With a low pH and possible hypoxemia it is well recognised that one may encounter multi-organ dysfunction in relation not only to brain but other organs including the heart.

As cardiotocography (CTG) is routinely used antenatally in an attempt to detect fetal distress, it seemed a natural continuum that these abnormalities should persist in the early post-natal period. With that in mind I looked at heart rate variability in the same group of infants in which I had examined EEG and suck patterns. There was no statistically significant difference either between those with overt encephalopathy and those who were normal or between those with a pH ≤ 7.0 and those with pH 7.01-7.25.

This does raise some interesting points. Infants who had a cord pH value ≤ 7.0 had EEG abnormalities and a sub-optimal suck response but did not have heart rate variability changes. Therefore neurological manifestations appeared to occur in the absence of any cardiovascular manifestations.

This study has proven that cord pH measurements are useful and instructive. They are particularly significant when values are ≤ 7.0. My findings show that in this latter group there are EEG and suck pattern changes. While these may not have any long-term clinical significance they do indicate that extreme acidosis is undesirable even in the absence of overt encephalopathy.

CHAPTER 1

INTRODUCTION

1.1   Setting the Thesis in Context

I initially became interested in the issue of perinatal acidosis and the outcome when I was a Senior House Officer in perinatal medicine at The National Maternity Hospital, Dublin. I was perplexed as to why acidosis at birth appeared to affect only occasional infants while most emerged unscathed. I felt it was an area worthy of further research and investigation.

Neonatal encephalopathy (NE) is a condition in the term infant characterised by a spectrum of severity ranging from grade I to grade III (Sarnat HB, Sarnat MS, 1976). Grade I is associated with mild abnormal neurological behaviour, Grade II manifests as seizures and Grade III as seizures and stupor. Almost all infants with Grade I and most with Grade II make a complete recovery. For infants with Grade III there is a substantial risk of death or severe neurological disability.

There is continued uncertainty about the relationship between acidosis at birth and the risk of developing NE. From published data at the National Maternity Hospital, it would appear that once the cord pH is < 7.0 the risk of NE increases significantly (National Maternity Hospital Annual Reports 1982, 1983). The incidence of NE is 10% in infants with a cord pH 7.1-7.25 and 40% in infants with a cord pH < 7.0 (Table 1.1).

The purpose of my thesis was to examine the relationship between acidosis at birth in term infants and the potential consequences in terms of altered neurophysiological and cardiovascular responses. In particular, I

wished to determine the level of acidosis secondary to asphyxia an infant can withstand without demonstrating physiological consequences. It was also envisaged that the research would illustrate the threshold level of acidosis in infants required to cause sub clinical or clinical manifestations.

1.2   Define its Relationship to Other Work in the Field

During the late 1970's until early 1990's a large series of studies were published both from the United Kingdom and America highlighting the specific manifestations of perinatal hypoxia (Dennis J, 1978; Gilstrap LC et al, 1989; Goldaber KG et al, 1991; Low JA, 1988; Minchomn P et al, 1986; Nelson KB, Emery ES, 1993; Weber T, Hahn-Penderson S, 1979; Winkler CL et al, 1991Yudkin PL et al, 1987). Based on all this literature and in the face of significant litigation a task-force comprisedof obstetricians and neonatologists from New Zealand, Australia and America published guidelines in 1999 for defining a causal relationship between acute intra-partum events and cerebral palsy (Mac Lennon A, 1999). Within their template they clearly define that the umbilical arterial cord pH value must be ≤ 7.0 with a base excess ≥ -12mmol/L, for

perinatal asphyxia to be deemed the cause of neurological damage.

Others expanded on the work of Monod (1972) and showed that in the case of perinatal hypoxia an early EEG recording was a very useful tool in the prediction of long-term outcome (Eyre JA et al, 1983; Grigg-Damberger MM et al, 1989; Hellstrom-Westas L et al, 1995; Holmes GL et al, 1983, 1993; Lombrosso CT, 1985; Watanabe K et al, 1980; Wertheim D et al, 1994). Burst suppression, electrographic seizures and isoelectric recordings were all associated with a very poor outcome and as a test had a very high sensitivity and specificity. They also showed that in the face of critically ill infant a normal EEG recording had a high correlation with a normal long-term outcome.

These findings allowed the EEG to be used as an objective tool, in clinical decision making. For example if an infant consistently had burst suppression or iso-electric patterns on his early EEG recordings then a decision could be made to withdraw ventilatory support. In contrast if the EEG was normal one could legitimately continue aggressive management.

1.3 Important Points about Treatment

This thesis on the relationship between acidosis at birth and altered neonatal neurophysiological and cardiovascular responses is now more relevant than previously because newer modalities of treatment are emerging.

Hitherto treatment of infants with encephalopathy was largely of a supportive nature including management of seizures, blood pressure, and electrolyte imbalance and glucose haemostasis.

Research over the last five years has shown that active intervention in the face of encephalopathy is now possible with the application of hypothermia (Edwards AD *et al*, 1995;Thoresen M *et al*, 1997)

Brain cooling studies are showing some promising results for a proportion of infants who have suffered asphyxia. One of the important issues will be trying to determine which infants will benefit from the therapy. It's my aspiration that the work I've undertaken will help to give new insight into this complex relationship between acidosis, asphyxia and encephalopathy.

Table 1.1   Relationship between cord pH values and clinical outcome in infants born in The National Maternity Hospital 1982 & 1983

Cord pH	Infants	Clinical NE*	Deaths	Abnormal follow-up
7.1-7.25	118	12	5	3
7.0-7.1	45	6	3	0
<7.0	25	10	6	4

*NE denotes Neonatal Encephalopathy

CHAPTER 2

ACIDOSIS

2.1 Introduction

In 1955, Virginia Apgar and colleagues published an article looking at the relationship of mental or motor development to the condition at birth (Apgar V et al, 1955). She noted that in the literature up to that date, one of four approaches was used to examine these infants.

i)   The observation of a neurological defect in a child and tracing his history back to the time of birth;

ii)   The notation of central nervous system symptoms or trauma at the time of birth and following the survivors for several years;

iii)   The observance of asphyxia or apnoea at birth with similar follow-up visits, and

iv)   The recording of clinical events at the birth of an unselected series of infants and tracing their future development.

In Virginia Apgar's study they employed a fifth approach, that of prospectively recording objective data relating to oxygenation in an unselected series of infants and following their subsequent course (Apgar V et al, 1955). Over a two year period they took blood samples from infants immediately after birth and at several intervals thereafter. They then measured the oxygen levels in the blood samples and divided the infants into those that were anoxic and those that were not. They found a worse neurodevelopmental outcome in the anoxic group.

Animal studies have provided some important data in relation to this. For example, when the uterine artery blood flow is reduced in sheep, PO_2

levels in the umbilical vein and artery fall long before a decompensation reaction, in which oxygen supply to the tissues is impaired. The supply is maintained because the arteriovenous difference stays the same, although the total levels in both will fall. Therefore the fall in PO_2 is an early part of the process. As fetuses become hypoxic (but not until the umbilical venous PO_2 drops below two standard deviations from the normal mean), they begin to develop a mixed respiratory and metabolic acidosis. In chronic hypoxia, there is no value in using the base excess, or in considering the resulting acidosis as metabolic or respiratory acidosis. Carbon dioxide and lactic acid begin to increase at the same time, after the PO_2 has dropped below the normal range for gestational age. (The Placenta).

In 1961 Erich Saling developed the technique for fetal blood analysis from the scalp of the fetus during labour (Saling E, 1962). This was the first direct approach to the fetus and was the crystallization point of perinatal medicine. The original publication was classified as a citation classic by The Institute of Scientific Information in 1984. In 1960, he performed the first blood gas analysis from the central circulation to determine the effectiveness of resuscitation methods in the newborn. In 1961 he together with Damasackhe, introduced a rapid method to measure the blood oxygen saturation in micro samples. Using Saling's technique a scalpel or stylette is passed through the cervix to make a small incision in the fetal scalp. A sample of blood is then collected in a capillary tube and analysed to determine its acid-base status (pH value). Saling found that about half the cases with slowing of the fetal heart had normal fetal scalp pH values. He recommended the introduction of fetal scalp blood sampling into clinical practice, as a means of making continuous fetal heart rate monitoring more specific (Saling E, 1964).

The hydrogen ion is the primary constituent of all acids. Acids are a by-product of cellular metabolism. The pH is a chemical symbol used to express the negative logarithm, or p, of the hydrogen ion concentration, in a given solution (Lynam LE, 1990). As it is the negative logarithm, a lower pH indicates a higher hydrogen ion concentration or acidemia. Conversely, a higher pH is consistent with a lower hydrogen ion concentration, or alkalemia. The pH scale ranges from 0-14. A neutral pH is 7.0, a pH less than 7.0 indicates acidity and a pH greater than 7.0 indicates alkalinity (Miller BF, 1978).

Under basal circumstances, body fluids are somewhat alkaline. Blood pH is maintained within a narrow range of 7.35 to 7.43 by a dynamic balance between carbon dioxide (CO_2) and bicarbonate ($HCO3^-$).

A favourable pH is essential to normal enzyme function within the body. As enzymes affect the rate of metabolism, some reactions are hastened and others slowed or cease in the presence of an unfavourable pH (Guyton AC, 1987).

Acidemia or alkalemia may also lead to changes in blood vessels or cell membranes, resulting in precarious oxygenation of myocardium, brain or other vital organs. A sustained pH below 7.0 or above 8.0 is generally considered incompatible with survival (T.E.OH, 1990).

Table 2.1   Comparison of pH value and hydrogen ion concentration
[H+]

pH value	[H+] (nmol/L)
6.80	158
6.90	126
7.00	100
7.10	79
7.20	63
7.30	50
7.40	40

It is important to appreciate that pH is a logarithmic function of the hydrogen ion concentration. Thus, a fall in pH from 7.3 to 7.2 is not as significant as a pH fall from 7.1 to 7.0. In the latter case there are twice as many free hydrogen ions generated. It is obvious from the table above (Table 2.1) (T.E.OH, 1990) that once the pH is below 7.0 the hydrogen ion concentration is twice normal (100nmol/L Vs 50nmol/L). However not all infants born with pH values of 7.0 and below are asphyxiated.

The diagnosis of intrapartum fetal asphyxia requires a blood gas and acid base assessment. The important question is the threshold of a metabolic acidosis beyond which fetal morbidity and mortality may occur. Umbilical vein and artery acid-base measurements at delivery represent valuable reference points of asphyxia exposure during labour. The umbilical vein reflects the effectiveness of maternal fetal blood gas exchange, while the umbilical artery reflects the acid base status of the fetus. As carbon dioxide and metabolites are transported from the fetus to the mother via the umbilical arteries, the oxygen levels and pH values are

lower, while carbon dioxide levels are higher in the umbilical arteries compared with the umbilical vein (MacKenna BR et al, 1997).

Table 2.2   Normal umbilical cord blood gas values.

	Umbilical Vein	Umbilical Artery
PH	7.31	7.24
PO_2 (kPa)	4.5	3.1
PCO_2 (kPa)	5.7	6.4

The increased frequency of uterine contractions during labour results in an accumulation of carbon dioxide and thus a gradual fall in the fetal pH in the first stage of normal labour (0.016units/hr) and a more rapid fall in the second stage (0.12units/hr) (Weber T et al, 1979). A respiratory acidosis then becomes part of normal labour. The placenta cannot hyperventilate and any reduction in the fetal placental blood flow, with cord compression and episodes of bradycardia, leads to a rapid carbon dioxide accumulation which quickly disappears with the first breaths of air.

Metabolic acidosis is the hallmark of intrapartum asphyxia and gives information on the cellular energy balance. In adults the base deficit (BD) can be calculated from the blood compartment (BD blood), but in the fetus and neonate this is incorrect as the calculation is unduly influenced by a high PCO_2 and a relatively increased extra cellular fluid (ECF) (Rosen KG et al, 1991; Siggard-Andersen O, 1971).

The increase in carbon dioxide results in the production of more H_2CO_3 in the red blood cells which dissociates into H^+ and HCO_3^-. The H^+ load is

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buffered by hemoglobin, and there is an increased concentration of HCO_3^- ions which leave the red blood cells and enter the plasma. This creates a HCO_3^- gradient between the plasma and the interstitial fluid so that HCO_3^- ions leave the plasma for the interstitial fluid. Thus, there is a net loss of HCO_3^- from the plasma that causes an apparent metabolic acidosis in the blood compartment and an increase in BD blood. This is particularly relevant in the fetus as there is always a mixed acidosis (both a respiratory and metabolic component) in cases of birth asphyxia. Furthermore, the fetus has a relatively large ECF compartment compared to an adult, so relatively more HCO_3^- is lost from the blood compartment before equilibrium is reached with the ECF. Siggaard-Andersen showed that the influence of a high PCO_2 could be avoided if the BD was calculated in the extra cellular fluid compartment (BDECF) and in 1971 produced an acid-base chart which allowed the calculation of BDECF (Siggard-Andersen, 1971). In cases of moderate mixed cord artery acidemia (pH <7.20) there is an average difference of BD blood and BDECF of 30% with BD blood constantly giving the higher BD (Rosen KG et al,1991).

Both the peripheral and central organs produce lactic acid during intrauterine asphyxia. A peripheral tissue metabolic acidosis develops sooner than a central metabolic acidosis. Both these organs contribute to systemic acidemia but it is not possible to separate the contributions made by each. However, once the BDECF shows a substantial increase (>12mmol/L) it is more likely that there is a central tissue component (Greene KR et al 1995). The Plymouth analysis of 1,840 cord acid-base data have shown that a significant metabolic acidosis does not occur until the pH falls to less than 7.05 (Greene KR et al, 1995).

The arteriovenous difference in cord blood provides information on the timing and possible cause of the oxygen deficiency (Roemer VM et al,

1976; Yudkin PL et al, 1987). Rosen (Rosen KG et al, 1991) demonstrated that the BDECF arteriovenous differences were 3.4+/- 2.3 mmol/L (mean +/- standard deviation) in cases with cord entanglement as compared with 1.1 +/- 1.25mmol/L in acidotic cases without cord entanglement. In the Plymouth analysis, the arteriovenous difference in uncomplicated deliveries ranged from 0.03 to 0.15 pH units and from BDECF –1.5 to 0mmol/L (Greene KR et al, 1995).

While carbon dioxide can diffuse rapidly across the placental membranes, hydrogen and lactate take much longer to equilibrate (Rooth G, 1957). Thus, in a steady state situation, while PCO_2 and therefore pH may differ, there should only be a small difference in the arteriovenous BDECF. In hypoxemia of acute onset, the cord artery shows a bigger change simply because the placental ECF compartment needs to be saturated before cord vein shows the same pH or BDECF values as the artery. The cord vein acid-base status is primarily that of the placenta. Since oxygen flow to the placenta is well maintained it could serve as an initial "sink", and not until the fetal H^+ load becomes significant would there be a cord vein acidemia.

Many levels of pH are presently used to define cord artery acidosis (7.20, 7.15, 7.11) but most of these are unrealistically high (Gilstrap LC et al, 1989). Increasing evidence from large studies, demonstrates that there is little association with neonatal mortality or morbidity and adverse long-term outcome, until the cord artery pH levels are less than 7.05 and particularly less than 7.00 (Gilstrap LC et al, 1989; Goldaber KG et al, 1991; Winkler CL et al, 1991). A publication from Low has demonstrated that the incidence of neurological symptoms in the neonatal period and neurodevelopmental deficits at one year, is related to substantial metabolic acidemia (Low JA, 1988), but the picture is far from as clear.

2.2 Background Data from the National Maternity Hospital

The National Maternity Hospital has been routinely performing cord blood pH analysis in high-risk deliveries since 1976 following the work of Saling in the late 1960's (Saling E, 1962, 1964). In the early 1980's data were reported looking at the outcome of infants in relation to their cord blood pH values (National Maternity Hospital, Annual Reports, 1982, 1983). Table 1.1 demonstrates that once the arterial pH value falls below 7.0 the rate of cerebral dysfunction and death increase significantly .

In 1985, The National Maternity Hospital published a large series –The Dublin Trial- of 12,964 infant-mother pairs in a randomised controlled trial of intra-partum foetal heart rate monitoring, using cord pH values of <7.2 as a sign of foetal distress (MacDonald D et al, 1985). Since then, all high-risk deliveries (~1,000/year) have cord bloods taken and analysed for pH, bicarbonate, oxygen, carbon dioxide and base excess. Gosta Rooth (Rooth G, 1956, 1957) established normal values for cord bloods in the 1950's. It is commonplace to divide low cord pH values at birth (perinatal acidosis) into mild pH 7.1 - 7.25, moderate pH 7.0 - 7.1 and severe <7.0. Only a very small proportion of infants have a cord pH value <7.0 (~4%), yet not all of these infants are clinically unwell and a proportion of the less acidotic infants (7.0 - 7.25) show clinical signs of asphyxia and develop neonatal encephalopathy. From our data collected over the last three years on low risk deliveries (spontaneous vaginal delivery/elective section with normal CTG) we found that <1% (0.9%) of "low-risk" babies have a pH value less than 7.0 (Impey L et al, 2003). The mean arterial cord pH was 7.24 and the mean venous cord pH was 7.31. The challenge is to find the pH threshold, which a newborn infant can safely tolerate, and aim to keep all infants above this value.

2.3 Energy Metabolism And Lactate Production

Normal cellular energy metabolism may be disrupted by hypoxic-ischemic injury. Adenosine triphosphate (ATP) is the principal high-energy phosphate in which energy is stored. When glucose is converted to pyruvate by glycolysis, only two molecules of ATP are generated. This represents a relatively inefficient use of energy potential. However, under aerobic conditions, oxidation of this pyruvate yields 34 further molecules of ATP for each molecule of glucose metabolized. Anaerobic conditions, by precluding this oxidation, force the less energy-efficient process of production of lactate. When ischaemia is added to hypoxia, brain acidosis increases because tissue lactate cannot be removed and tissue CO_2 is not adequately buffered by bicarbonate (Little WJ, 1862). However there is considerable biological leeway before hypoxia will impinge on the infant's cerebral function. The ATP levels must fall to less than 25% of normal before neurones start being injured and under 10% of normal, before neuronal death occurs.

Myers and his colleagues have attempted to reproduce the events of human perinatal asphyxia in the monkey (Myers RE, 1972). They demonstrated two patterns of brain damage associated with asphyxia. Acute total asphyxia produced neuronal necrosis of brain-stem nuclei, and partial prolonged asphyxia produced necrosis in the cerebral hemispheres. These animal models have proved to be useful paradigms of human asphyxia. Investigators have tried to pinpoint certain markers that may predict asphyxia during the perinatal period. One of the most objective markers is the fetal pH value. The severity of the metabolic acidosis may reflect either the duration or the intensity of the asphyxial event. Although fetal acidosis is widely taken to be a pH < 7.20, a more reliable value indicating the possibility of neurological compromise is < 7.05 or < 7.0 (Levene MI, 1995). In fact a recently published consensus statement from

the Australian, New Zealand and American perinatal societies, states that for cerebral palsy or any neurological compromise to be attributed to a perinatal event the pH must be <7.0 and the base excess > -12mmol/L (Mac Lennon A, 1999).

In biological terms there must be a spectrum between the completely abnormal and the completely normal. The point at which abnormality becomes manifest is a matter of contention. PH and acidosis offers an opportunity as increasing acidosis and hydrogen ion concentration are an indication of hypoxemia. The value at which injury is more likely than not to happen is important in terms of prognosis and management.

2.4 Placental Physiology: Oxygen Transport

Placental oxygen transfer depends on maternal and fetal placental blood flows and the oxygen carrying capacities of the maternal and fetal blood. According to the Fick principle, uterine oxygen delivery is equal to uterine blood flow, times the arteriovenous difference of oxygen content across the uterine circulation. When uterine blood flow is decreased, with uterine contractions, maternal exercise or smoking, the continued rapid diffusion of oxygen out of the maternal blood results in a fall in uterine venous oxygen content and thus an increase in arteriovenous difference, resulting in increased oxygen extraction. This increase in extraction maintains uterine oxygen delivery until uterine blood flow falls by more than 50%. Thus increased uterine extraction results in a wide margin of safety for oxygen delivery to the uterus under normal circumstances.

Under some circumstances, there may be further adaptation to maintain uterine oxygen delivery. For example, maternal exercise results in haemoconcentration, thus increasing oxygen delivery to the uterus despite a decrease in uterine blood flow. The shift in the maternal hemoglobin

oxygen dissociation curve caused by increased temperature and acidosis also improves oxygen delivery and may contribute to this adaptation.

Fetal oxygen delivery is similarly a product of the umbilical blood flow and the arteriovenous differences for oxygen content across the umbilical circulation. Once again reduced umbilical blood flow, such as may be seen in cord compression, results in no change in umbilical venous oxygen content because of rapid oxygen diffusion across the placenta. If fetal oxygen demand is unchanged, this results in a fall in foetal PO_2 as the reduced amount of oxygenated fetal blood mixes with the deoxygenated blood reaching the heart. This in turn results in decreased umbilical arterial PaO_2, increasing the arteriovenous difference for oxygen across the placenta and thus increasing fetal oxygen extraction. Once again, there is a relatively wide margin of safety, and acute falls in umbilical blood flow result in no change in fetal oxygen uptake until the flow is reduced by more than 50%.

Essential to this remarkable capacity to increase oxygen extraction in the face of decreased blood flow, to either side of the placenta, is the capacity of the placenta to allow rapid gas transfer. Since oxygen transfer across the placenta is by diffusion down a concentration gradient, persisting rapid transfer requires no decrease in concentration gradient.

To achieve this, oxygen must be unloaded from the maternal haemoglobin efficiently, and removed on the fetal side of the placenta by rapid binding to foetal haemoglobin. In this way, the high affinity of fetal haemoglobin for oxygen helps maintain transfer and allows increased extraction as the supply decreases, if either uterine or placental blood flow decrease. If the affinity of haemoglobin on the fetal side of the placenta is decreased, (e.g. by exchange transfusion with adult haemoglobin), or has reduced carrying

capacity (e.g. fetal anaemia), the capacity to increase extraction of oxygen in the face of reduced supply is decreased and thus the margin of safety is decreased. Likewise, increased maternal haemoglobin oxygen affinity, (e.g. maternal haemoglobinopathies), or reduced maternal haemoglobin oxygen carrying capacity, (e.g. carbon monoxide from maternal cigarette smoking displacing oxygen from maternal haemoglobin), will result in no acute decrease in fetal oxygenation, but a reduced margin of safety in the face of any changes in blood flow.

It is possible that other adaptive mechanisms contribute to the capacity of the fetus to increase oxygen extraction from the maternal circulation when required. For example fetal hypoxemia may result in a rise in umbilical venous tone and pressure, thus potentially opening previously under-perfused fetal/placenta vessels and increasing the available exchange area in the placenta for oxygen extraction. When oxygen supply or umbilical blood flow is reduced chronically, it is also likely that placental oxygen demand is reduced in order to improve fetal oxygen supply. If decreased oxygen supply is maintained, there appears to be a gradual reduction in fetal oxygen uptake, within a resultant reduction in the oxygen gradient across the placenta and reduced placental oxygen transfer, e.g. intrauterine growth retardation.

Experimental literature that addresses the question of a critical threshold for oxygen saturation in the fetus is limited. One such study was performed by Richardson and colleagues in the late 1980's. Eleven un-anesthetized fetal sheep (126 to 135 days gestation) were studied during prolonged and graded hypoxemia (Richardson B et al, 1989)

Preductal fetal lamb arterial and sagittal venous blood samples were analysed for oxygen saturation, blood gases, pH and lactate. As the time

course of fetal hypoxemia was variable among animals, results were grouped according to foetal arterial oxygen saturation, with a mean value obtained for each animal within a grouping for multiple values. Graded reductions in arterial oxygen saturation (SaO_2) resulted in little change in arterial pH until the saturation fell to values between 30% and 40%, at which point a mild lactic metabolic acidosis was apparent. When the SaO_2 fell to values below 30%, an obvious significant lactic acidosis was present.

From these data, it can be concluded that a critical threshold of oxygen saturation exists for fetal hypoxia. The critical threshold value of oxygen saturation, above which the fetus does not demonstrate significant acidosis, is approximately 30%.

Richardson later expanded this study to include additional animals and measurements of electro-cortical activity, and breathing movements during prolonged and graded hypoxemia (Richardson B et al, 1992) Again, because the time course of fetal hypoxemia was variable among animals, results were grouped according to fetal arterial oxygen saturation, with a mean value obtained for each animal within a grouping for multiple values. Fetal electro-cortical activity was assigned by visual analysis into periods of high voltage (100 to 200 mVlts), low voltage (less than 50 mVlts) and intermediate voltage (50 to 100 mVlts). Fetal breathing movements were defined as repeated negative deflections in tracheal pressure of greater than 2mmHg lasting for more than 30 seconds.

Arterial pH did not change significantly in the fetal sheep until the fetal oxygen saturation was between 30% and 40%. In this range, 3 of the 14 animals began to show a developing metabolic acidosis with a related fall in base excess. With arterial oxygen saturation below 30%, all animals

except one showed a metabolic acidosis with variable falls in arterial pH noted. This acidosis was accompanied by physiological changes in electro-cortical activity, electro-ocular activity and breathing movements.

The percent time spent in low voltage electro-cortical activity averaged 53% +/- 1.4% with fetal SaO_2 > 60% and showed a marginal decrease with SaO2 between 30% and 60%. With SaO_2 <30% and a metabolic acidosis apparent in all but one animal, the fraction of time spent in low voltage electro-cortical activity decreased to 35% +/- 4.1% on average. The results of this expanded study demonstrate that arterial oxygen saturation at or near 30% is a critical threshold level. Below this the fetal sheep is highly likely to experience metabolic acidosis and its associated consequences and above this acidosis is not present nor are its consequences present.

A reasonable approach to defining the boundary between normal safe values of oxygen saturation and abnormally low values is to define the critical threshold at or below the 5th percentile of the SpO_2 distribution in fetuses with normal-outcome labour. Examining 87 normal outcome human fetuses the mean $FsPO_2$ in the 45% to 50% range and relatively few values below 20% or above 70% were observed. Only 3% of measured values were less than 30% and would appear to represent a critical threshold between "normal" and "abnormal" in a population of human fetuses with a normal outcome (Swedlow D, 1997).

In a 1989 Technical Bulletin, the American College of Obstetricians and Gynaecologists states "the most common indication for fetal scalp blood sampling is to assess a potentially abnormal fetal heart rate pattern". They also note that a scalp pH of less than 7.20 is considered abnormal and generally is an indication for some type of medical or surgical

intervention. The purpose of a multi-centre trial was to quantify the predictive agreement (if any), between $FSpO_2$ and fetal scalp pH, when used to assess fetal status during periods of non-reassuring fetal heart rate patterns in labour.

The $FspO_2$ was then plotted against the scalp pH and the sensitivity and specificity of $FspO_2 < 30\%$ as a predictor of scalp pH < 7.20 was assessed.

2.5 Summary

This chapter explains the basics of acid-base metabolism and the history of fetal pH sampling. It highlights the experience The National Maternity Hospital has both in the technique of umbilical cord blood sampling and the effects of acidosis on its population. This chapter also demonstrates the lack of knowledge in the literature on the spectrum of acidosis that the neonate can cope with before asphyxia ensues. Above all, it highlights the need for further research to designate a threshold for perinatal acidosis.

CHAPTER 3

RESEARCH QUESTION

3.1 General

This research was undertaken in order to address the complex relationship between acidosis at birth, asphyxia and abnormal neurophysiological and cardiovascular responses. It attempted to identify what underlying mechanisms determined whether an infant at risk due to asphyxia would emerge normal or would have sequelae.

It was hoped that the research would enable us to identify what degrees of asphyxia the infant can safely cope with. Also I wished to find out what levels of asphyxia the infant began to manifest physiological changes.

It was anticipated that the research would give obstetricians guidance about what levels of acidosis they can tolerate in their clinical practice, while on the other hand neonatologists would get better insight as to which babies are likely to need more careful monitoring and intervention.

3.2 EEG

Since the first human EEG recording in 1929 by Berger, EEG technology has evolved rapidly from the simple 6 leads and paper pen recordings in the first half of this century to advanced 30-lead digital recordings with incorporated video recordings, which allow one to establish the clinical behaviour of the infant when EEG abnormalities are present e.g. seizures and outrule things which are not abnormal e.g. movement artefact. The majority of neonatal works in the last 20 years especially in relation to hypoxic-ischaemic injury have used amplitude integrated EEG technology (CFM), which only uses 3 electrodes.

One aim of this thesis was to assess the EEG patterns and characteristics in high-risk term neonates who are acidotic at birth. I used 30-lead digital EEG as the gold standard; in the hope that it would allow me to detect more subtle abnormalities not previously reported and perhaps establish a spectrum of EEG patterns across the pH range. Also as aforementioned, detailed EEG recordings have a higher sensitivity and specificity than CFM. I proposed that once the pH value at birth falls below 7.0 regardless of the clinical condition of the child that EEG abnormalities would be present representing sub-clinical encephalopathy. I chose 30-lead digital EEG as my main mode of investigation, as all research to date has shown that it has the highest predictive value (both negative and positive) of all tests currently available (Hanrahan, 1997). It is also the most accurate and reproducible tool available early in the neonatal period therefore the best for assessing early acidosis and how it is affecting the neonate.

3.3 Manometric Recording

The ability of a term infant to suck early in the neonatal period has been used as a guide to their neurological status.

Ineffective sucking during this time is seen as a poor prognostic marker, for long-term neurodevelopmental outcome. It is clear that there is little objective research to confirm or refute this observation and to date no research that assesses neonatal sucking in the face of perinatal acidosis and/or encephalopathy. Also, none of the published literature to date has measured and recorded the all-important negative intra-oral pressure.

In this thesis I set out to measure the integrity of the neonatal suck reflex by objectively measuring the intra-oral amplitude, frequency and patterns of sucking in newborns that are acidotic at birth and compared the results

of those who were clinically normal to those who were encephalopathic. I
expected to see a reduction in amplitude and frequency in the more
encephaloapathic infants (Sarnat stage III) compared to the less
encephalopathic (Sarnat I/II) and the clinically normal.

I also postulated that there would be a difference between the more
profoundly acidotic (pH≤7.0) neonates compared to the moderately/mildly
acidotic infants (7.01-7.25).

3.4 Heart Rate Variability (HRV)

The most significant intrapartum fetal heart rate parameter to predict the
development of significant acidemia is the presence of minimal/absent
variability for at least one hour as a solitary abnormal finding or in the
conjunction with late decelerations in the absence of accelerations
(Williams KP, Galerneau F, 2003). Electronic fetal heart rate monitoring
is routinely used in high-risk deliveries in an effort to detect fetal distress
early and so prevent or at least minimise the sequlae i.e. HIE.

Recent studies have demonstrated reduced heart rate variability in
neonates with impending sepsis (Griffin MP, Moorman JR, 2001; Griffin
MP et al 2003). As a third and final adjunct to this study I measured the
HRV of the neonates recruited. I expected to see a reduction in HRV
values in those infants with severe acidosis i.e. pH≤7.0 and an even more
marked reduction in those with clinical HIE. For consistency and accurate
comparisons of results I chose 5-minute epochs during the QS portion of
the EEG recording for analysis. A geometric time domain method was
used in the mathematical calculations giving results of mean and median
RR intervals as well as SDNN.

CHAPTER 4

ELECTROENCEPHALOGRAM

4.1 Background EEG principles

EEG examines by means of scalp electrodes the spontaneous electrical activity of the brain. Tiny electrical potentials, which measure millionths of volts, are recorded, amplified and displayed on channels of a pen recorder. Low and high frequency filters remove unwanted signals such as muscle artefact and mains interference.

The waveforms recorded are thought to reflect the activity of the surface of the brain, the cortex. This activity is influenced by the electrical activity from the brain structures underneath the cortex.
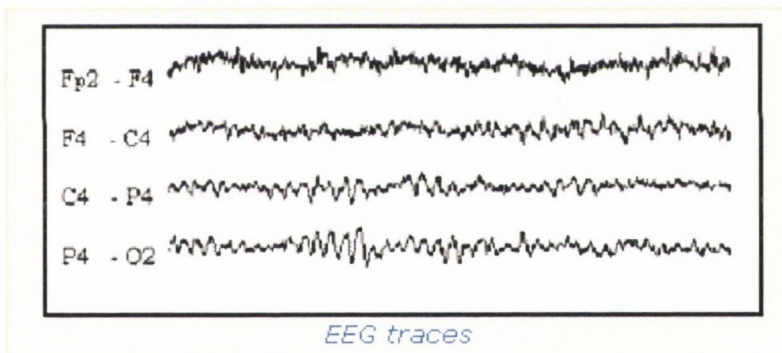
EEG traces

Fig 4.1   Sample of EEG traces

The nerve cells in the brain produce signals that are called action potentials. These action potentials move from one cell to another across a gap called the synapse. Special chemicals called neurotransmitters help the signals to move across the gap. There are two types of neurotransmitters, one will help the action potential to move to the next cell, the other will stop it moving to another nerve cell. The brain

normally works hard to keep an equal amount of each of these neurotransmitters in the brain.

EEG activity is quite small, measured in microvolts (μV) with the main frequencies of interest up to approximately 30 Hertz (Hz).

4.1.1 Electrodes

Small metal discs called electrodes are placed on the scalp in special positions (Fig 4.2). The recordist who measures the head using the International 10/20 System identifies these positions. The system of electrode placement is referred to as the 10/20 system because the distance between bony points, i.e. inion to nasion, is divided into lengths of either 10% or 20% of the total, and the electrodes placed at each distance. Each electrode site is labelled with a letter and a number. The letter refers to the area of brain underlying the electrode e.g. F - Frontal lobe and T - Temporal lobe. Even numbers denote the right side of the head and odd numbers the left side of the head.

Fig 4.2   System of electrode placement

There is a great variety of electrodes that can be used. The majority are small discs of stainless steel, tin, gold or silver covered with a silver chloride coating. These normally have a lead attached. Alternative methods consist of a cap in which the electrodes are already embedded. The following essential electrodes should be used in recording neonatal EEG:

- Standard 10-20 EEG electrodes
- Eye movement (right and left EOG electrodes)
- Submental EMG electrodes (i.e. two electrodes under the chin)
- 2 ECG electrodes placed on the chest
- Respiration electrode placed below the navel

4.1.2 Montages

EEG machines use a differential amplifier to produce each channel or trace of activity. Each amplifier has two inputs.

An electrode is connected to each of the inputs.

Amplifier principles
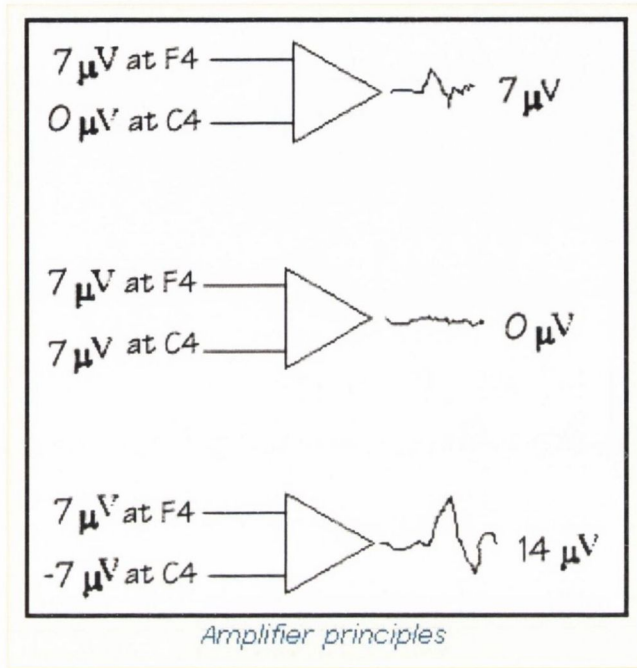
Fig 4.4   Schematic representation of amplifier principles

Differential amplifiers measure the voltage difference between the two signals at each of its inputs. The resulting signal is amplified and then displayed as a channel of EEG activity.

Differential amplifier
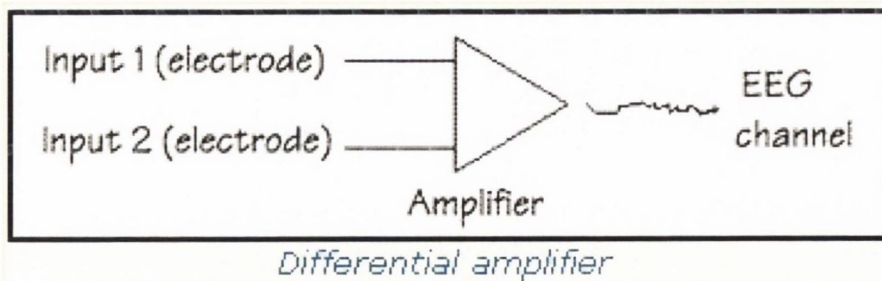
Fig 4.5   Schematic representation of differential amplifier principles

The manner in which pairs of electrodes are connected to each amplifier of the EEG machine is called a montage. Each montage will use one of three standard recording derivations, common reference, average reference or bipolar.

With common reference derivation each amplifier records the difference between a scalp electrode and a reference electrode. The same reference electrode is used for all channels. Electrodes frequently used as the reference electrode are A1, A2, the ear electrodes, or A1 and A2 linked together.

Common reference derivation
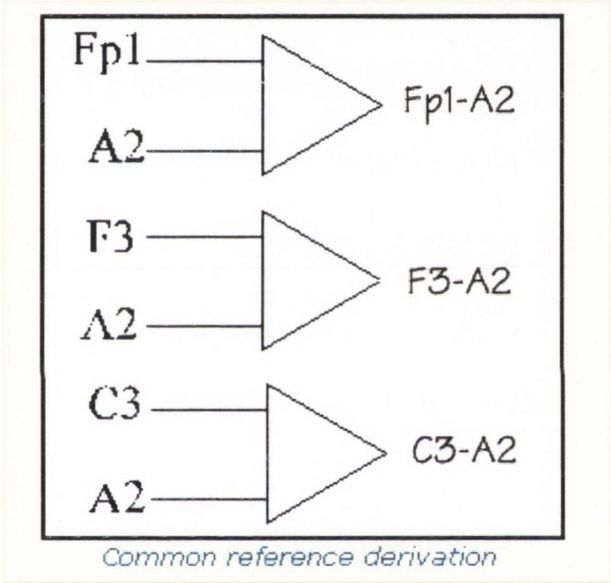
Fig 4.6   Schematic representation of common reference derivation

In average reference derivation activity from all the electrodes are measured, summed together and averaged before being passed through a high value resistor. The resulting signal is then used as a reference electrode and connected to input 2 of each amplifier and is essentially inactive. All EEG systems will allow the user to choose which electrodes are to be included in this calculation.

Average reference derivation
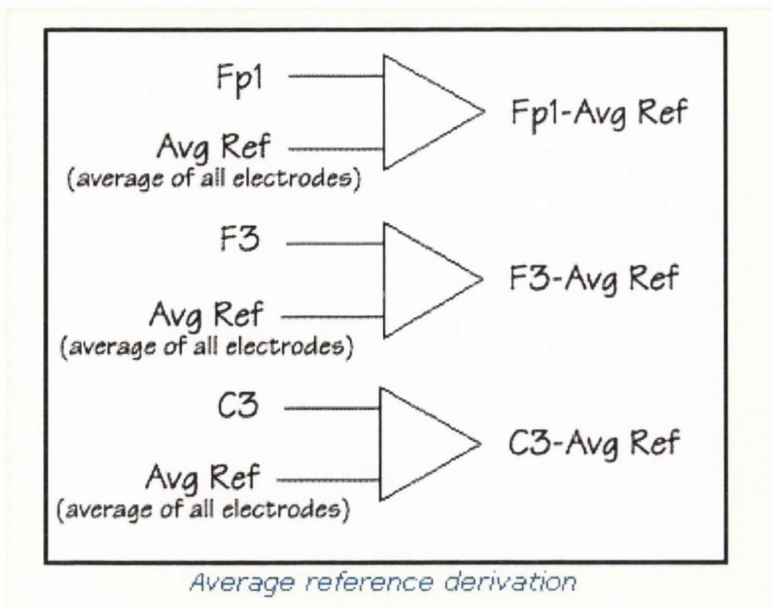
Fig 4.7   Schematic representation of average reference derivation

With bipolar derivation electrodes are sequentially linked together usually
in straight lines from the front to the back of the head or transversely
across the head. For example the first amplifier may have electrodes FP1
and F3 connected to it and the second amplifier F3 and C3 connected to it.

4.1.3 Analogue EEG instruments

Conventional analogue instruments consist of an amplifier, a
galvanometer and a writing device. A galvanometer is a coil of wire inside
a magnetic field. The output signal from the amplifier passes through the
wire causing the coil to oscillate. A pen mounted on the galvanometer
moves up and down each time the coil moves. The pen draws the trace
onto paper moving below it.
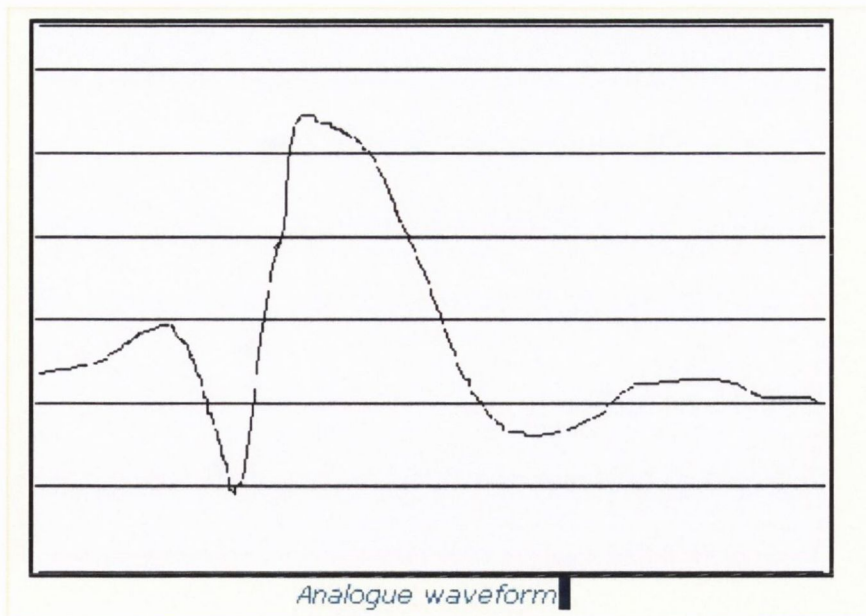
Analogue waveform

Fig 4.8   Analogue waveform

The amplifier output is controlled by high and low frequency filters and sensitivity controls. The high and low frequency filter values will set the window within which the EEG activity is recorded. This is known as the bandwidth.

The sensitivity controls the size of the activity displayed. For example a sensitivity of 10 μV/mm means that a signal with an amplitude of 100 μ V will produce a 1 cm vertical deflection.

The speed at which the paper moves on will also affect the appearance of the waveforms.

4.1.4 Digital EEG instruments
A digital EEG system converts the waveform into a series of numerical values. This process is known as Analogue-to-Digital conversion
The values can be stored in the computer memory, manipulated and then redisplayed as waveforms on a computer screen.

The rate at which the waveform data is sampled in order to convert it into a numerical format is known as the sampling rate. The sampling rate is usually expressed in Hz, for example 240 Hz is 240 times per second. The minimum acceptable sampling rate is 2.5 times greater than the highest frequency of interest but most digital EEG systems will sample at 240 Hz. Some recordings which involve recording activity directly from the brain surface, may have activity of a higher frequency, for example 200 Hz. Therefore some digital EEG systems will have optional sampling rates of 480 Hz available.

Sampling at rates lower than this will mean that when the signal is converted back to analogue form, it will not resemble the original waveform .

Sampling rate of 50 Hz
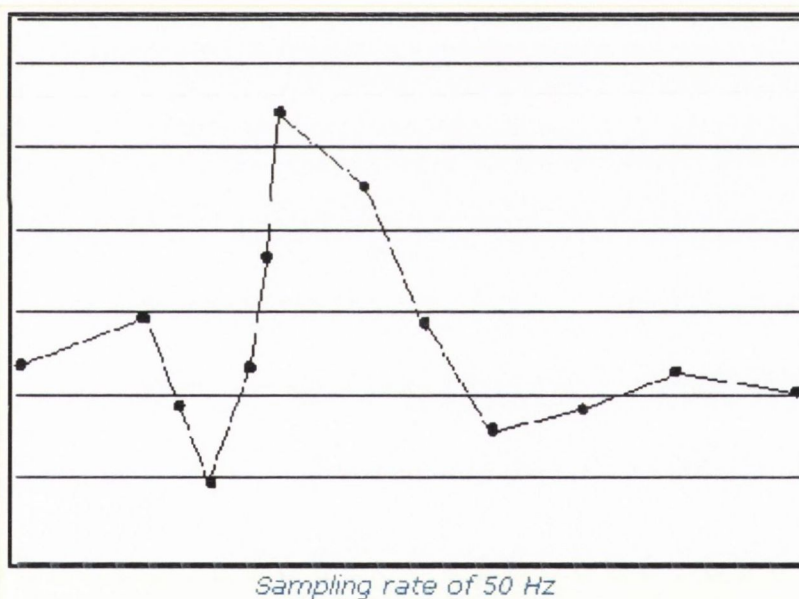
Fig 4.9   Schematic representation of an EEG sampling rate of 50 hertz (Hz)

A second factor that affects the accuracy of the waveform is sampling skew. Sampling skew occurs when all channels are not sampled simultaneously. Many digital EEG systems sequentially sample from channel 1 onwards. The time lag between sampling of each channel is

known as sampling skew. To reduce the sampling skew, some digital systems use burst mode sampling. This increases the speed between successive channels sampling in order to reduce the amount of sampling skew.

A third factor that affects the accuracy of digital EEG waveforms is the display. The accuracy of a monitor display depends on the number of points or pixels that are available. The number of pixels available is referred to as the screen resolution. Screen resolution is described in numbers that represent the pixels available in the horizontal and vertical axis.

A VGA display has a resolution of 640 x 480 pixels while a monitor with a Super VGA display will have a screen resolution of around 1024 x 768 pixels. A typical page of EEG contains 10 seconds of data. A digital EEG system, sampling at rates of 240 Hz will need to display 2400 samples horizontally for each recording channel. The highest screen resolutions available today do not have enough pixels to match the number of data samples. Systems that draw every other sample or every third sample in order to match the screen resolution will have the effect of reducing the sampling rate and displaying incomplete data. An accurate digital system will draw two data samples per screen pixel. This means that all data points can be displayed and sampling rates will not be decreased.

EEG signals that have been digitised can be manipulated to change the montage 'on-line' at the time of recording or 'off-line' after the recording is completed. This 'remontaging' is accomplished by recording all EEG channels with a common reference electrode. Regardless of the montage used to display the data while it is being recorded, data is stored into the computer memory in common reference mode. This allows the data to be

displayed using different montages at a later time. Since digital systems store the analogue signal as numerical values, remontaging is a simple subtraction process which results in cancellation of the common reference.

An example is shown in the next figure. The reference electrode A1 is common to both channels on input 2. It has the identical value in each channel. Remontaging these two channels together into one new channel is by subtraction which mathematically will cancel the value at the reference electrode. The resulting channel will therefore display the potential difference between F3 (input) 1 and F4 (input 2).

4.1.5 EEG Activity

EEG activity can be broken down into 4 distinct frequency bands: Beta activity > 13 Hz; Alpha activity 8 Hz-13 Hz; Theta activity 4 Hz-7 Hz; Delta activity < 4 Hz

Beta activity is a normal activity present when the eyes are open or closed. It tends to be seen in the channels recorded from the centre or front of the head. Some drugs will increase the amount of beta activity in the EEG.
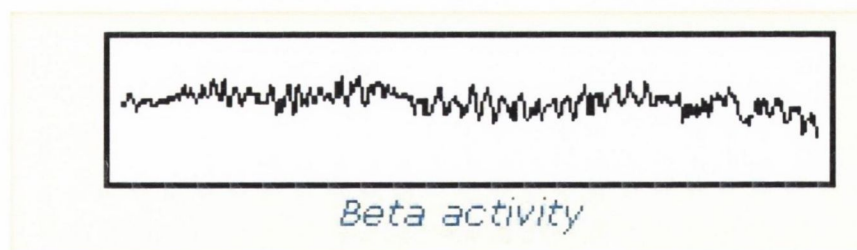
Beta activity

Fig 4.10   Sample of an EEG recording of beta activity which has a frequency of > 13Hz

Alpha activity is also a normal activity when present in waking adults. It is mainly seen in the channels recorded from the back of the head. It is fairly symmetrical and has amplitude of 40 μV to 100 μV. It is only seen when the eyes are closed and should disappear or reduce in amplitude when the eyes are open.
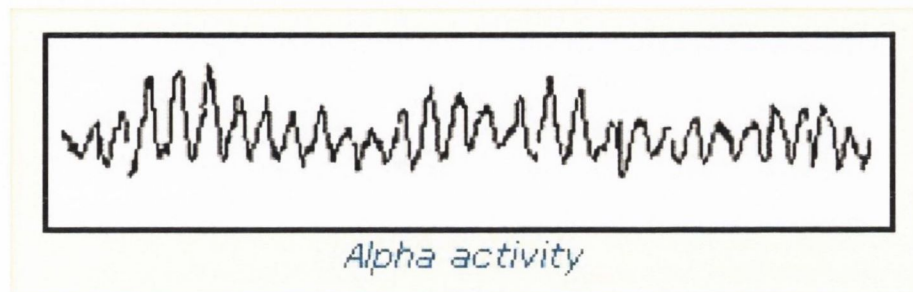
Alpha activity

Fig 4.11   Sample of an EEG recording of alpha activity, which has a frequency of 8 to 13Hz

Theta activity can be classed as both a normal and abnormal activity depending on the age and state of the patient. In adults it is normal if the patient is drowsy. However it can also indicate brain dysfunction if it is seen in a patient who is alert and awake. In younger patients, theta activity may be the main activity seen in channels recorded from the back and central areas of the head.
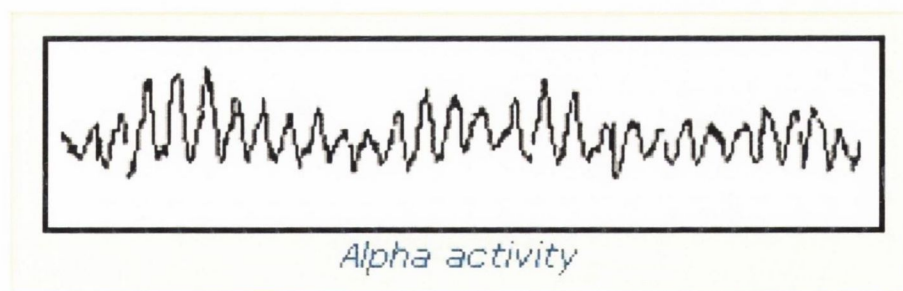
Alpha activity

Fig 4.12   Sample of an EEG recording of theta activity which has a frequency of 4 to 7 Hz

Delta activity is only normal in an adult patient if they are in a moderate to deep sleep. If it is seen at any other time it would indicate brain dysfunction. Abnormal activity may be seen in all or some channels depending on the underlying brain problem.
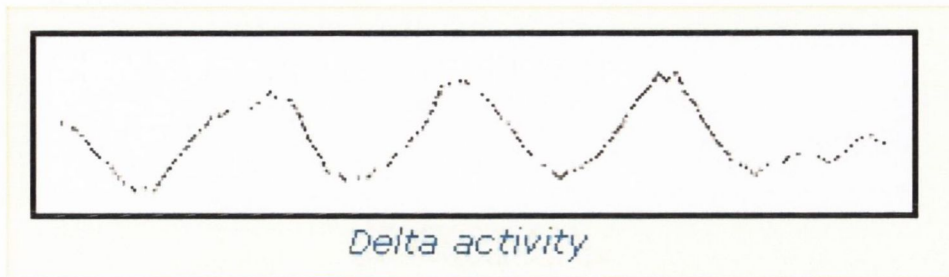
Fig 4.13   Sample of an EEG recording of delta activity which has a frequency of < 4Hz

There are a number of other waveforms which tend to be a little more specific to certain conditions. For example spike and wave activity indicates a seizure disorder and may be seen in the EEG even if the patient is not having an epileptic seizure. Other epileptic conditions may be diagnosed if spikes or sharp waves are seen.
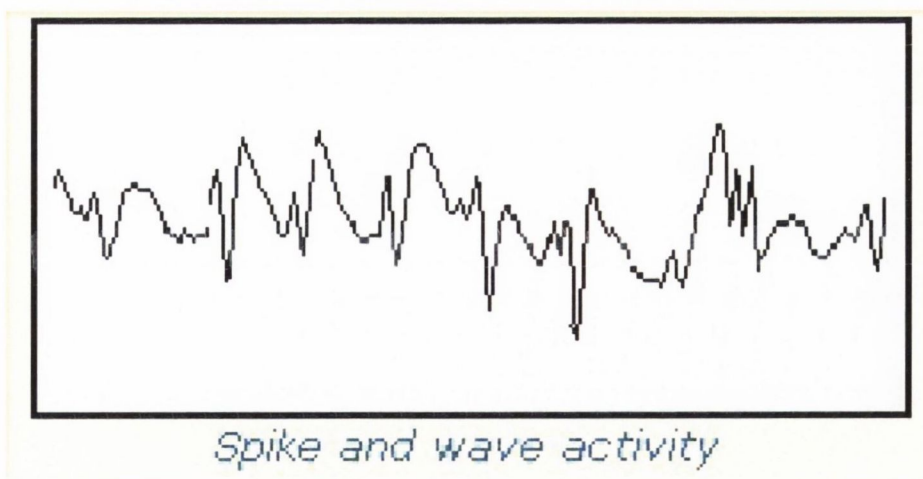
Fig 4.14   Sample of an EEG recording demonstrating seizure/spike and wave activity

Triphasic waves are sometimes seen if the patient has severe liver or kidney disease that is affecting brain function. These are just brief descriptions of some of the simpler waveforms that may be seen in any one EEG recording. Combinations of any of the above patterns are possible which can make interpretation of the record difficult. Abnormal activity is not always specific to a particular condition and may suggest a few different diagnoses.

4.1.6   Neonatal EEG activity

Abnormalities in the neonatal EEG are not classified as epileptic. They generally fall into the following categories.

- Excessive sharp waves
- Encephalopathic
- Neonatal seizures (not epileptic)

The term newborn typically has three states.

- Awake (AW)
- Active sleep (AS)
- Quiet sleep (QS)

If all three states are not recorded, then the EEG study is incomplete. It typically takes approximately one hour to record all three states. Frequent annotation by the technician is essential during the EEG. All neonatal EEGs should be recorded using video if possible. This allows visualization of movement artefact.

There are several technical considerations when recording from a small scalp:

- High skin resistance opposing low-resistance scalp-electrode contact.
- The importance of the state of activity (awake or quiet versus active sleep) that can be selectively bound to certain aspects of pathology.
- It is important to annotate the tracing with particular attention to the presence/type of eye movements, facial movements, respiration: regular or irregular, sucking, crying, grimacing, etc.,
- The necessity for extra cerebral monitors in routine recordings, including at least electrooculogram (EOG), respiration and electrocardiogram (ECG).
- Only a reduced number of scalp electrodes, preferably never exceeding the set of a 16-channel recording, are applicable.
- A low time constant (0.25-0.6 secs) is preferable to record the low-frequency background activity.
- Slow paper speed maximizes the slow background and degree of interhemispheric synchrony.

In the awake state (AW) the EEG background generally consists of theta activity of low amplitude, some sharp waves, irregular respirations, phasic EMG from sub-mental (chin) electrodes and irregular eye movements.

In active sleep (AS) the EEG generally consists of theta activity of low amplitude, some sharp waves, irregular respirations, no EMG activity from sub-mental (chin) electrodes - patient becomes atonic- and rapid Eye movements (REM)

In quiet sleep (QS) the EEG generally consists of a trace alternant pattern, regular respirations, no eye movements, no EMG activity from sub-mental (chin) electrodes, in reality there is always some EMG activity, just less in QS. During QS there is an increased likelihood of abnormalities, such as excess of sharp waves or seizure activity emerging. No neonatal EEG recording is complete without this portion.

Frontal sharp waves are normal when in moderation, between 36 and 44 weeks. Trace alternant pattern which occurs in quiet sleep consists of high voltage mixed frequency activity followed by low amplitude activity for 3-5 seconds. The low amplitude interval can become longer in deeper sleep, however excessive prolongation is considered abnormal. It occurs typically between 36 to 42 weeks +/- a few weeks and is therefore a specific finding in the early EEG of a term neonate. Delta brushes can be seen in quiet sleep at 32 – 35 weeks gestation. Posterior predominant delta is a normal finding in a term baby.

4.1.7 Abnormalities of the neonatal EEG

Typical abnormalities seen in the neonatal EEG are seizures, excessive sharp waves, especially if persistently focal, decreased amplitude of background EEG, poor state differentiation, asynchronous EEG activity, burst suppression and excessive discontinuity of background.

Over the past several decades, electroencephalography (EEG) in newborn infants has acquired value as a serial non-invasive screening tool for those at high risk of antenatal or perinatal injuries. The brain dynamics and connectivity in different states (awake/sleeping) can be explored as well as a whole range of acute or chronic cerebral disorders.

Such findings often reveal information on pre-symptomatic or sub clinical conditions. The EEG prognostic value at an age of continuous development is often higher than at later ages; thus reassurance can be offered in the context of seemingly catastrophic damage. The continuous changes that accompany the brain's early development are often associated with striking changes in EEG patterns over short periods of time. This adds complexity to the EEG interpretation, frequently discouraging potential users.

Given the close relationships between some morphological aspects of the developing brain and the EEG, gestational age (GA) can be readily estimated by EEG criteria with an appreciation error or +/- 1 week. In fact the CNS development of the immature brain proceeds at about the same rate during foetal life and in the extra uterine environment (Dreyfus-Brisac, 1956). The physiological substrate for these early EEG change in patterns is unknown but is probably derived from cortical generators that are highly influenced by sub cortical (primarily thalamic) afferent input.

4.2 Clinical application and interpretation.

One of the major roles of EEG is as an aid to diagnose epilepsy. Abnormal patterns such as spikes, sharp waves and/or spike and wave complexes can be seen. The type of activity and the area of the brain that it is recorded from will assist the physician in prescribing the correct medication for that type of epilepsy.

Patients with epilepsy that cannot be controlled by medication will often have surgery in order to remove the damaged tissue. The EEG plays an important role in localising this tissue. Special electrodes can be inserted through the cortex or alternatively a grid of electrodes placed directly on the surface of the cortex. These recordings, often called Long Term

Monitoring for Epilepsy (LTME), can be carried out for periods ranging from 24 hours to 1 week. The EEG recorded will indicate which areas of the brain should be surgically removed.

EEG studies can also be used in patients who are deeply unconscious, to distinguish between brain death and possible reversible conditions.

Electro cerebral inactivity (ECI) or electro cerebral silence (ECS) is defined as no EEG activity over 2 μV in amplitude when recording from electrodes on the scalp, that are 10 cm or more apart.

Using the 10/20 International System of electrode placement, the average distance between electrodes in an adult is 6 to 6.5 cm. Activity recorded using these distances and at a normal display sensitivity may suggest ECS. However if the same activity was recorded using longer inter-electrode distances, some activity might be seen. Therefore some double distance electrode linkages are recommended for example FP1-C3, F3-P3 and C3-O1.

Display sensitivities of a minimum of 2 μV/mm are required. However digital EEG systems have the added advantage of having sensitivity values of 1.5 and 1 μ V/mm. This 50-100 % increase in sensitivity will allow a more confident assessment of the presence or absence of a 2 μ V signal.

The EEG is also used to investigate other conditions that may affect brain function such as strokes, brain injuries, liver and kidney disease and dementia.

4.2.1   EEG Recording

The EEG recording can last from anything between 15 minutes to 1 hour or longer depending on the situation. Typically the patient will be lying down or sitting relaxed in a chair. Most of the recording is taken with the eyes closed, although the patient will be frequently asked to open them for short periods. The neonatal EEG is recorded with the infant lying down. It is best performed post feed, firstly, to allow the infant to settle and to decrease movement artefact and secondly to allow capture of all sleep states. It is necessary to adjust for mains interference if the EEG has to be performed in a neonatal intensive care unit (NICU), especially if the infant is ventilated, as ventilation artefact can make it almost impossible to interpret the EEG.

Most patients will be asked to carry out a period of deep breathing for approximately 3 minutes. This may produce some abnormal activity which would not be seen while the patient is relaxed. The physiological effect of deep breathing is to increase the amount of carbon dioxide (CO_2) being removed from the bloodstream. This fall in CO_2 produces a fall in blood pressure and at the same time blood vessels in the brain become constricted. This reduces blood flow and the delivery of oxygen and glucose to the brain. This in turn may produce some abnormal brain activity not seen in the resting record.

Photic stimulation is also carried out. A strobe lamp is placed 30 cm from the patient's eyes. Brief flashes of light (2 - 5 seconds in duration) at a number of different flash frequencies are delivered to the patient with both eyes open and eyes closed. A continuous flash with increasing and decreasing flash frequencies is sometimes used. Some patients who are sensitive to flashing lights may show abnormal activity in the EEG. Photic stimulation is not performed in the neonate.

Throughout the test the recordist is constantly annotating any patient movements or tasks that they are carrying out on the record.

Other signals may also be recorded in conjunction with the EEG such as heart rate (ECG), respiration, eye movements (EOG), and muscle activity (EMG). These are important components of the neonatal EEG.

4.2.2 EEG Analysis

The EEG reports consist of a number of different sections. The recordist may prepare a report describing the type of activity seen in the record together with changes produced by deep breathing and photic stimulation. They will also comment on the patient's state during the recording. The physician will then interpret these changes with regard to the medical problem being investigated.

With an increase in the number of long recordings being carried out, many departments make use of detection algorithms such as spike and seizure detection. Although it is still necessary for the clinician to review the complete record, such programmes will mark and highlight sections of interest. The most efficient method of implementing these algorithms is for the detection to be carried out on-line.

Other methods of analysing EEG data include Power Spectrum Analysis. A Fast Fourier Transform (FFT) is performed on sections of EEG data to determine the power content of the four main frequency bands. The resulting waveforms can be displayed as a brain map, which will show the scalp distribution of the power within each frequency band. The amplitude of the different waveforms at a single point can also be displayed in a similar format. This type of display provides a more objective analysis of the EEG activity compared to a subjective visual analysis by a physician.

4.2.3 Video monitoring

Simultaneous video monitoring of the patient during the EEG recording is becoming more popular. It allows the physician to closely correlate EEG waveforms with the patient's activity and may help produce a more accurate diagnosis.

Domestic video recorders and cameras can be connected to an EEG machine using a time code generator. This records an accurate time signal onto the videotape. When the videotape and EEG are reviewed together the two signals are accurately synchronised together.

Video monitoring is always used for Long Term Monitoring recordings as the patient is unattended. The patient may also have an event button connected to the EEG machine so that times when the patient thought they were having an epileptic attack can be easily identified.

4.2.4 Sleep Studies

The EEG is frequently used in the investigation of sleep disorders especially sleep apnoea. EEG activity together with other physiological signals such as heart rate, airflow, respiration, oxygen saturation and limb movement are measured simultaneously. These recordings are usually carried out overnight although some sleep studies can be carried out in the department during the day under strictly controlled conditions.

The EEG record can be broken down into epochs which are normally of 30 seconds duration. Using the EEG activity, each epoch is classified into one of 5 sleep stages. This is displayed visually as a Sleep Histogram. Respiration and airflow are used to look for periods of apnoea which occur when the patient stops breathing. These are then correlated with the

sleep stage in which they occurred and the level the oxygen desaturation during the apnoea.
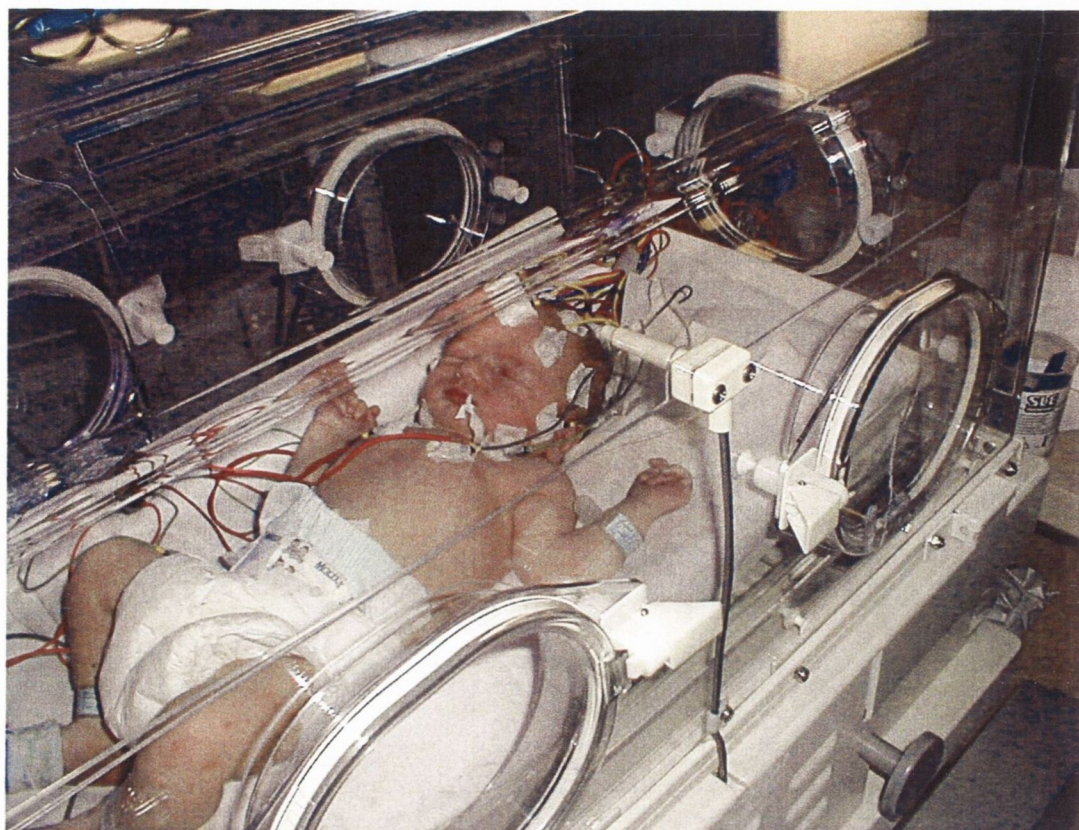
Fig 4.3   A term neonate with scalp and ancillary electrodes in place.
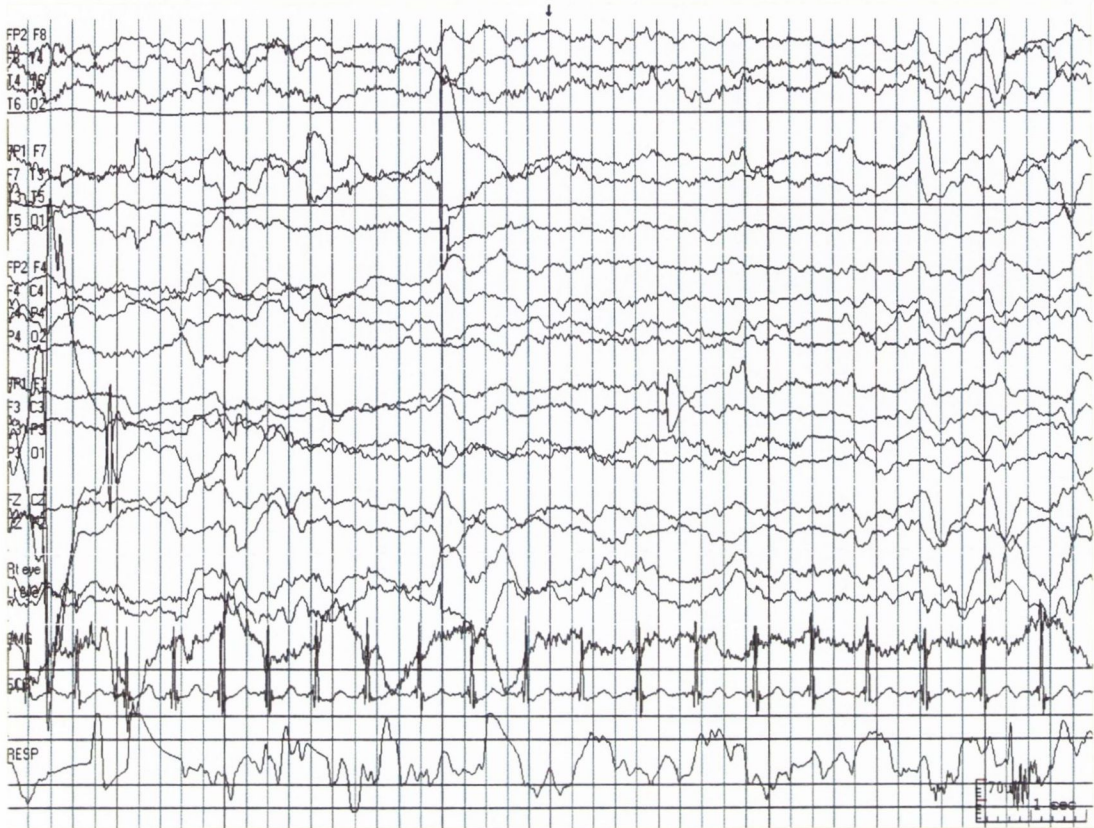
Fig 4.15   Sample of an awake EEG in term infant
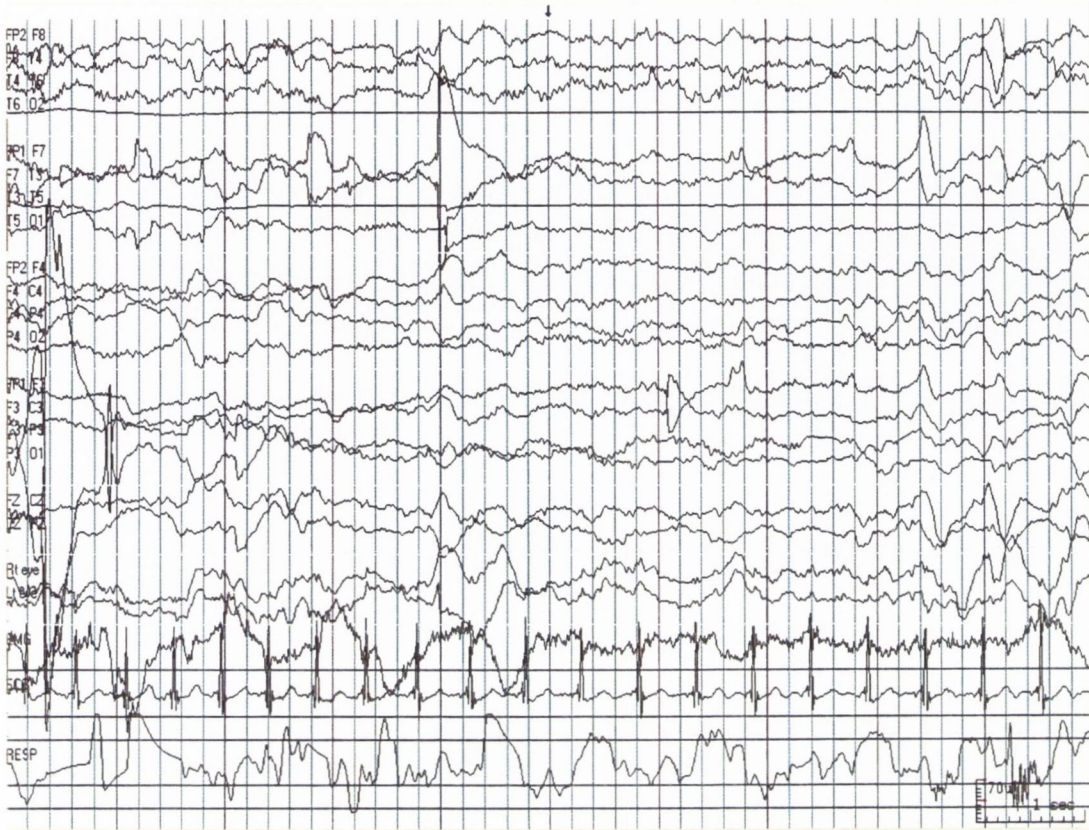
Fig 4.15   Sample of an awake EEG in term infant

Fig 4.16   Sample of an active sleep EEG in a term infant

Fig 4.17   Sample of a quiet sleep EEG in a term infant

4.3 History of the neonatal EEG

The first documentation of an EEG recording is in the British Medical Journal in 1875 by Caton (Caton R, 1875). He reports his work on apes and rabbits demonstrating for the first time that there is spontaneous electrical activity coming from the brain (Fig 4.18).

In 1929 Berger made the first report of EEG recordings in humans (Berger, 1929). He examined thirteen subjects including himself, his own son and a bald medical student. Berger explains in great detail how he started with 555 electrodes placed all over the body and gradually reduced the number to three scalp electrodes (2 occipital and 1 central). He demonstrated that the waveforms were not from cerebral blood vessels, respiration or scalp muscle artefact, but from the brain itself (Fig 4.19).

It was not until 10 years later that Smith made the first recording of EEGs in infants, followed by a larger series published a year later by Lindsley (Lindsley DB, 1936, Smith JR, 1937). They both noted that the frequency (i.e. the number of waves per second) was much slower in infancy (4-5/sec). Lindsley also demonstrated that increasing brain weight curves from infancy to childhood corresponded linearly with increasing frequency of EEG. However EEG frequency did not correlate with intelligence quotient.

While some work was published by Gibbs in the 1940's in relation to cortical development and the use of EEG to demonstrate this (Gibbs FA, 1949), the main body of early neonatal EEG research was carried out by Hughes. In 1948 Hughes and colleagues published data on EEG recordings on 113 normal, full term, sleeping infants in the first days of life (Hughes JG et al, 1948). He demonstrated that the

electroencephalographic patterns of normal, full term, sleeping infants are characterised by a lack of sustained rhythm and by two peak frequencies occurring in waves of 1 to 2 per second and of 5 to 10 per second (Fig 4.20). In general the higher the frequency of the waves the lower the amplitude, and the amplitude of the waves in the newborn is less than that encountered in older infants, children and adults. His observations gave objective evidence from the electrical standpoint of the functional cortical immaturity known to exist in the newborn. He then went on in 1949 to describe that the electroencephalogram of the wide-awake neonate is characterized by a decidedly flattening effect (Hughes JG, et al 1949). Not only does rhythmic activity almost cease, but also there is practically no amplitude to the tracings, which appear as essentially straight lines with random fluctuations of low amplitude. Finally in 1951 Hughes described the EEG patterns in 22 normal premature babies (Hughes JG et al, 1951). His findings indicated that in premature infants cortical electrical activity from the frontal region is better developed in regard to frequency, amplitude and rhythm than are the brain potentials from other areas of the cortex. This observation was contradictory to what would be expected from the prenatal maturation of the human cortex.

All of the above EEGs were recorded using six scalp electrodes- 2 frontal, 2 pre-central and 2 occipital (Fig 4.20).

In the 1950's and 1960's major breakthroughs were made in the clinical use and application of the neonatal EEG. Kellaway showed that certain patterns on the neonatal EEG were indicative of disease, especially seizures (Kellaway P, Fox BJ, 1952). It was Drefyfus-Brisac and Ellingson who demonstrated for the first time that the neonatal EEG pattern changes with different sleep states (Drefyfus-Brisac C et al, 1956, Ellingson RJ, 1958) Then in the early 1970's Monod showed that not only could the early EEG be used to diagnose pathology but that certain patterns could predict long-term neurodevelopmental outcome (Monod N et al, 1972). For example "burst suppression" was synonymous with a very poor outcome.

During the 1980's and 1990's a large series of reports were published both form the United Kingdom and North America highlighting the specific clinical situation of perinatal hypoxia. They expanded on the work of Monod and showed that in the case of perinatal hypoxia early EEG was a very useful tool in the prediction of long-term outcome (Connell I et al 1989; Dennis J, 1978; Ellingson RJ, 1979; Eriksson M, Zetterstrom R, 1979; Grigg-Damberger MM et al 1989, Holmes GL et al, 1983, 1993; Lombrosso CT, 1985, Minchom P et al 1986; Murdoch-Eaton D et al, 1993, Volpe JJ, 2001, Watanabe K et al 1980; Wertheim D et al 1994). Burst suppression, electrographic seizures and bioelectric recordings were all associated with a very poor outcome and as a test had a very high sensitivity and specificity. They also demonstrated that even in the face of a very critically ill child a normal EEG recording had a high correlation with a normal long-term outcome.

These breakthroughs allowed the EEG to be used as an objective tool, in clinical decision making in the emotionally charged situation of a critically ill yet normally formed full-term infant. For example if a child consistently had burst suppresssion/iso-electric patterns on their early EEG recordings then a decision could be made to withdraw ventilatory support. In contrast if the EEG was normal one could legitimately continue intensive care management.

In the mid 1980's data was published on a new kind of EEG technology-amplitude integrated EEG (Aziz, Eyre). This allowed cot side recordings using only 3 electrodes. A myriad of work ensued using this technology and showed strong correlations with traditional EEGs (al-Naqeeb, Biagionoi, Hellstrom-Westas, Toet). However there are some limitations given one only uses three electrodes. This technology is only useful for detecting extreme abnormalities e.g. burst suppression, seizures etc., but would not have the ability to either detect subtle abnormalities, seizures in areas not covered by the electrodes or pinpoint abnormalities to specific areas of the brain.

This work using amplitude integrated EEG technology in the face of perinatal asphyxia culminated in 2001 with a large series by Biagioni and colleagues from the Hammersmith in London. His work showed that if one combines the use of early EEG and magnetic resonance imaging there is an almost 100% correlation with clinical outcome.

A chart kindly reprinted from a thesis by Dr. D. Hanrahan (table 4.1) highlights that early EEG is the only objective test which has high sensitivity and specificity early after the insult in perinatal hypoxic-ischaemic injury, therefore making it the gold standard in any clinical decision making to withdraw or continue intensive care (Hanrahan,1997).

sight, was one which he had localised by an entirely different method, viz., that of noting the variations in the electrical currents of the brain as caused by functional exercise.—Dr. FRASER and Dr. SMITH followed, and the latter expressed the general sense of the meeting in thanking Dr. Lauder Brunton for ably explaining Dr. Ferrier's views.

SECTION F. PHYSIOLOGY.
Wednesday, August 4th.

DR. BURDON SANDERSON, F.R.S., President, took the Chair at 2 P.M.

Transference of the Long Tendon of the Biceps Muscle from the Scapula to the Humerus in Chronic Disease of the Shoulder. By JOHN STRUTHERS, M.D., Aberdeen.—Dr. Struthers explained how the tendon, say in a rheumatic shoulder, being no longer of any use, was removed from the upper bone and joined on to the lower bone, by which its use was thereby to some extent preserved. The steps of this process were narrated, and the subject was further elucidated by the exhibition of specimens. Adhering to the lower bone by the effects of excited action, the part of the tendon within the joint, having become functionless, was seen in various stages of passing away, while the attachment of the lower bones, on which the muscle pulled, became gradually stronger till the adaptation was completed. Dr. Struthers remarked that this might be called a pathological process; but pathological processes were also physiological processes; and, he expected that in future, the study of these processes would throw much light on questions connected with the origin and adaptation of healthy structures.

Experiments on Change of the Bodily Temperature consequent on Section ... ., LL.D., F.R.S., London.

The Electric Currents of the Brain. By RICHARD CATON, M.D., Liverpool.—After a brief *résumé* of previous investigations, the author ga... ...ments on the brains of the rabbit and the monkey. The following is a brief summary of the principal results. In every brain hitherto examined, the galvanometer has indicated the existence of electric currents. The external surface of the grey matter is usually positive in relation to the surface of a section through it. Feeble currents of varying direction pass through the multiplier when the electrodes are placed on two points of the external surface, or one electrode on the grey matter, and one on the surface of the skull. The electric currents of the grey matter appear to have a relation to its function. When any part of the grey matter is in a state of functional activity, its electric current usually exhibits negative variation. For example, on the areas shown by Dr. Ferrier to be related to rotation of the head and to mastication, negative variation of the current was observed to occur whenever those two acts respectively were performed. Impressions through the senses were found to influence the currents of certain areas; e. g., the currents of that part of the rabbit's brain which Dr. Ferrier has shown to be related to movements of the eyelids, were found to be markedly influenced by stimulation of the opposite retina by light.

The Digestive Principle of Insectivorous Plants. By LAWSON TAIT, F.R.C.S.Ed., Birmingham. Mr. Tait communicated the results of cer-

BEVERIDGE, M.D., Aberdeen. The death of this man occurred almost immediately after his first descent for the season. There was no defect in the apparatus, and his companion who descended with him was unaffected; it could not, therefore, be due to deficient supply of air. On a previous occasion, this man had, under similar circumstances, nearly lost his life. It also was his first descent for the season. It was usual for divers on descending for the first time to experience a feeling of oppression and a sensation as if the head would burst. This, as a rule, passed very quickly away, and nothing further was observed in the way of discomfort till after leaving the water, when there was very often a sensation of giddiness, sometimes an attack of sickness, and in many cases a flow of blood from the nose and mouth. Most men after a few trials became accustomed to the work and suffered no inconvenience, but some did not do so, and always suffered in some way on leaving the water. These symptoms were undoubtedly due to the varying pressure on the vessels on the lungs, and in the above case had produced complete stoppage of the pulmonary circulation. This view was confirmed by the *post mortem* examination. The heart was large, pale, and flabby; its cavities were empty of blood; the lungs were intensely gorged with dark fluid blood. The air-tubes, beginning at the fauces, were much congested, dark purple in colour; and the smaller bronchi were partially filled with dark frothy blood. Other organs were also loaded with dark blood. The heavy pressure (in this case doubled) would cause partial stoppage of the lung-circulation, throwing back the venous blood on the right side of the heart, and thus inducing insensibility and suffocation, while the quick taking off of the pressure could allow all these vessels to fill to the utmost, thus producing the great gorging of all the bronchial surface, and the complete emptying of the cavities of the heart. In the discussion that ensued, several gentlemen expressed doubt as to the cause of the man's death, suggesting that, although one of the diving-bells was safe, the other might not have been so, and that this might not have been ascertained on account of the connecting-tube being out of order.

Thursday, August 5th.

Physiological Acoustics. By J. G. McKENDRICK, M.D., Edinburgh. —Dr. McKendrick gave a demonstration on physiological acoustics, with the view of illustrating the results of the researches of Helmholtz regarding the quality of musical sounds. After pointing out that Helmholtz had discovered that a musical note consisted, not of one tone, but of a series of tones, Dr. McKendrick proceeded to show this by means of an ingenious contrivance devised by Dr. Koenig of Paris. In a series of interesting experiments, it was shown how a tone could be decomposed, as it were, into its fundamental harmonics, and in this way an actual flame-picture of it be obtained.

Effect of Division of the Sympathetic Nerve of the Neck in Young Animals. By WILLIAM STIRLING, D.Sc., M.D., Edinburgh.—Dr. Stirling said that the division of the sympathetic nerve in the neck, for instance, of a young rabbit or dog was, in the first place, followed by the ordinary symptoms of the operation. As the animal grew, however, it was found that the ear of the side in which the nerve was divided grew more than that on the other side. The hair of the ear upon this side became stronger than on the opposite side; and, lastly, the temperature of the affected part continued higher than that of the other side for

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Fig 4.18   Copy of original article by Caton, 1875

Über das Elektrenkephalogramm des Menschen.

Von

Professor Dr. Hans Berger, Jena.

(Mit 17 Textabbildungen.)

Wie *Garten* [1], wohl einer der besten Kenner der Elektrophysiologie, mit Recht hervorgehoben hat, wird man kaum fehlgehen, wenn man jeder lebenden Zelle tierischer und pflanzlicher Natur die Fähigkeit zuschreibt, elektrische Ströme hervorzubringen. Man bezeichnet solche Ströme als bioelektrische Ströme, weil sie die normalen Lebenserscheinungen der Zelle begleiten. Sie sind wohl zu unterscheiden von den durch Verletzungen künstlich hervorgerufenen Strömen, die man als Demarkations-, Alterations- oder Längsquerschnittsströme bezeichnet hat. Es war von vornherein zu erwarten, daß auch im Zentralnervensystem, das doch eine gewaltige Zellanhäufung darstellt, bioelektrische Erscheinungen nachweisbar seien, und in der Tat ist dieser Nachweis schon verhältnismäßig früh erbracht worden.

Caton [2] hat bereits 1874 Versuche an Kaninchen- und Affenhirnen veröffentlicht, bei denen unpolarisierbare Elektroden entweder an der Oberfläche beider Hemisphären oder die eine Elektrode an der Hirnrinde, die andere an der Schädeloberfläche angelegt worden waren. Die Ströme wurden zu einem empfindlichen Galvanometer abgeleitet. Es fanden sich deutliche Stromschwankungen, die namentlich beim Erwachen aus dem Schlaf und beim Eintritt des Todes sich verstärkten, nach dem Tode schwächer wurden und dann vollständig schwanden. Schon *Caton* konnte nachweisen, daß starke Stromschwankungen bei Belichtung des Auges sich an der Hirnrinde einstellten, und er sprach bereits die Vermutung aus, daß unter Umständen diese Rindenströme zur Lokalisation innerhalb der Hirnrinde verwendet werden könnten.

Fleischl von Marxow [3] hat im Jahre 1883 zuerst beobachtet, daß bei verschiedenen Tieren bei Ableitung von zwei symmetrisch gelegenen

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[1] *Garten:* Die Produktion von Elektrizität. *Wintersteins* Handbuch der vergleichenden Physiologie 3. Bd., 2. Hälfte, S. 105.

[2] *Caton:* Brit. med. J. **2**, 278 (1875). Ref. Zbl. Physiol. 4, Nr 25 (1890). Nach *Bechterew:* Die Energie des lebenden Organismus. S. 102. Wiesbaden 1902.

[3] *Fleischl von Marxow:* Gesammelte Abhandlungen S. 410. Leipzig: J. A. Barth 1893 und Zbl. Physiol. 4 (1890).

Fig 4.19   Copy of original article by Berger, 1929
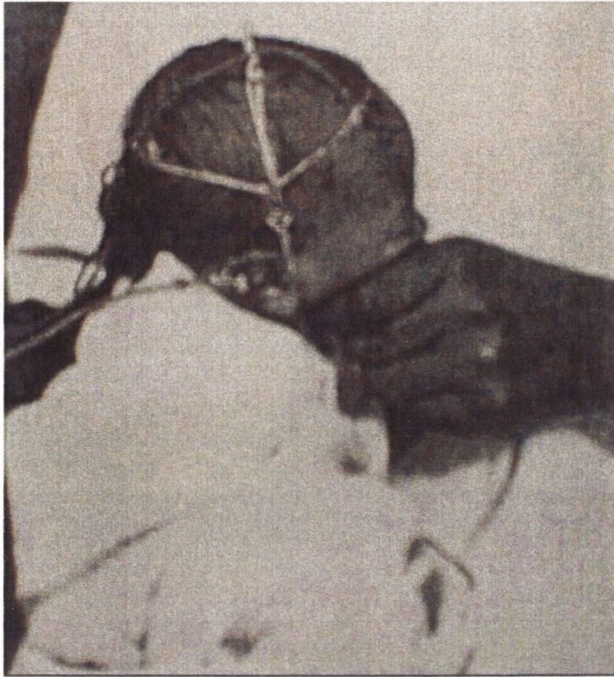
Fig 4.20   Copy of photo of infant using system of early neonatal electrode placement from original article by Hughes, 1948

Table 4.2   Key dates & names in the history of the Neonatal EEG

1875   Caton -1st EEG in rabbits and monkeys

1929   Berger-1st EEG in humans

1937   Smith- 1st EEG in infants

1938:   Lindsley-Electrical potentials in children

1948/49   Hughes-EEG of term newborn infants

1949   Gibbs-Growth of electrical activity

1951   Hughes-EEG of premature infants

1952   Kellaway-EEG diagnosis of pathology in infants during sleep

1955/56   Dreyfus-Brisac-EEG of term & premature infants

1957   Ellingson-EEG immediately after birth

1964   Dreyfus-Brisac-Normal and abnormal waking & sleeping
patterns

1970   Dreyfus-Brisac-Panel discussion on sleep cycles in newborn
infants

1972   Monod-Prognostic value of neonatal EEG

1973   Volpe-Neonatal seizures

1976   Sarnat-Neonatal encephalopathy following fetal distress: A
clinical & EEG study

1979   Lombroso-Interhemispheric synchrony close to full-term GA

1979   Eriksson-Neonatal convulsions

1980   Watanabe-Prognosis of EEG in newborns with perinatal
hypoxia.

1982   Holmes-Significance of reactive burst suppression following
asphyxia in full term infants.

1983   Eyre-Diagnosis of neonatal seizure by continuous recording &
rapid analysis of EEG.

1985   Lombroso-Neonatal EEG a review of normal & abnormal
findings.

1986   Aziz-Cotside EEG using computerised spectral analysis.

1987   Connell-Continuous EEG monitoring in the evaluation of echo dense ultrasound lesions

1989   Greisen-Discontinous EEG activity and periventricular brain injury in ill preterm neonates.

1989   Connell-Continuous EEG monitoring of neonatal seizures.

1989   Grigg-Damberger-Neonatal burst suppression its developmental significance

1990   Tharp-Intensive video/EEG monitoring of neonates

1993   Holmes & Lombroso-Prognostic value of background patterns in the neonatal EEG

1994   Wertheim & Dubowitz-Prognostic value of EEG after HIE

1994   Eaton-Changes in cerebral activity associated with acidosis in preterm neonates.

1995   Hellstrom-Westas-Predictive value of early EEG on outcome after severe birth asphyxia

1998   Biagioni-Prognostic value of abnormal EEG transients in preterm & full-term neonates.

1999   Toet-Amplitude integrated EEG 3 & 6 hours after birth in full term neonates with HIE

2001   Biagioni-Combined use of EEG & MRI in full-term neonates with acute encephalopathy.

CHAPTER 5

Suck Reflex

5.1 Background principles of the suck reflex

The newborn infant's suck is a primitive reflex developed at about 32 weeks gestation and matures throughout the period 32 to 40 weeks (Gewodb IH et al, 2001). In the first days of life oral feeding in the newborn is almost entirely reflexive, with rooting, latching, sucking and swallowing not appearing to require suprabulbar activity (Stevenson RD, Allaire JH, 1991). The rhythm regulators of oral feeding are principally represented in the nuclei ambiguus, solitarius and hypoglossus in the lower portion of the medulla and also in the nucleus trigeminalis. (Doty RW, 1965; Sumi T, 1964; Amri M et al, 1990; Jean A, 1990; Volpe JJ, 2001). Medullary neuronal injury is well described after hypoxic-ischaemic insults in the term newborn infant (Schachter F, Apgar V, 1959; Volpe JJ, 2001). Absence or poor suck is often observed in infants with hypoxic ischaemic insults. The absence of a suck response in a term infant is a worrying sign and indicative of significant neurological dysfunction. The time taken before teat feeding is established is accepted as a prognostic marker in infants with neonatal encephalopathy (Volpe JJ, 2001).

5.2 Previous studies analysing suck reflex.

The first documented studies looking at infant feeding and sucking patterns were in the mid 1950's by Andran and colleagues in Oxford and Sweden (Andran GM et al, 1958a). They first published a cineradiographic study of bottle feeding using barium suspension mixed with milk in the bottles and took films at 25/sec with the babies lying on a couch with their head and neck in lateral projection.

They examined three groups of children;

- Fifteen English children aged between 6 weeks and 6 months who were entirely bottle fed
- 20 Swedish babies aged between 1 hour and 10 days (mostly term breast fed
- 9 lambs and kid goats

They drew the following conclusions

- The influence of gravity is important in bottle-feeding. It ensures that the bulb of teat fills. If the hole in the teat is large enough milk drips into the mouth; when rigid teats are used this may be the only way the child can obtain an adequate milk supply.
- The lambs and kid goats take one teat full of milk with each jaw and tongue movement; the neck of the teat is completely occluded by approximation of the jaws and the contents of the bulb are expressed into the mouth by elevation of the tongue towards the soft palate, the tongue indenting the bulb from before backwards. Babies usually attempt this movement but in most instances are only partly successful; the teats normally supplied are too rigid and the hole too small.
- Following compression of the bulb of the teat by the squeezing action of the tongue, the lowering of the jaw and tongue must cause some degree of suction which may aid refilling of the bulb and it may also draw milk into the mouth; the amount of milk obtained in this manner may in favourable circumstances equal the amount obtained by expression.

- During the phase of compression of the bulb of the teat by elevation of the tongue in the forepart of the mouth there is also taking place simultaneously a lowering of the tongue behind the teat, which must cause some suction.

- Factors relating to the design of different teats have been considered.

- When milk is swallowed, naso-pharyngeal closure is made by elevation of the soft palate against the adenoidal pad on the roof of the epipharynx. The mode of closure is different from that seen in adults.

- The bolus passes through the pharynx on both sides of the superior laryngeal aperture. The larynx is closed as each bolus is expressed from the pharynx and reopened just before the next bolus enters.

Their second study was a cineradiographic study of breast-feeding (Andran GM et al, 1958b). They studied 41 healthy breast fed babies ranging in age from a few days to several months. They coated the mother's nipple and areola in a paste of barium sulphate in lanolin.

They drew the following conclusions

- The nipple is sucked to the back of the mouth and a teat is formed from the mother's breast.

- When the jaw is raised this teat is compressed between the upper gum and the tip of the tongue resting on the lower gum. The tongue is applied from the lower surface of the teat from before backwards, pressing it against the hard palate: the teat is reduced to approximately half its former width. As the tongue moves towards the posterior edge of the hard palate the teat shortens and becomes thicker.

- When the jaw is lowered the teat is again sucked to the back of the mouth and restored to its previous size.

- Each cycle of jaw and tongue movement takes place in approximately 1.5 seconds. The pharyngeal cavity becomes airless and the larynx closed every time the upward movement of the tongue against the teat and hard palate is completed.

- These movements are analogous to those seen in bottle-feeding: they suggest that the contents of the ducts or cisterns of the teat are expressed into the mouth.

- The influence of suction upon the flow of milk from the teat has not been established. It is considered that suction may be exerted during the phase of compression of the teat as the tongue is simultaneously lowered behind the teat.

- It is suggested that the teat is formed from the nipple and the adjacent areola and underlying tissues.

In a study on 43 cats that were decerebrated at the midcollicular level under temporary ether anaesthesia, Sumi and colleagues from Washington in 1964 showed that the neuronal mechanisms partaking in the regulation of the act of swallowing fell into three groups (Sumi T, 1964):

- Nerve cells in nucleus solitarius whose activity is modulated by afferent inflow from mucosa and deep structures of the oropharyngeal cavity

- Nerve cells in ambiguus and hypoglossal nuclei which control the motor act of swallowing

- Respiratory nerve cells

In 1965 Doty examined the neural organization of deglutition examining a large series of patients and reviewing all the literature, he drew the

conclusion that there are three separable components or neural control systems (Doty RW, 1965):

- The buccopharyngeal
- The oesophageal
- The gastroesophageal

In 1966 Kron demonstrated that infant sucking was affected by obstetric sedation (Kron RE et al, 1966). Brechtl published some more polygraphic data in 1967 but it was not until 1968 that Wolff published the first large series looking specifically at sucking in the young infant (Brechtl HFR et al, 1967; Wolff PH, 1968). The basic measures of sucking behaviour in these infants were extracted from polygraph records. He examined five groups:

- 40 controls who were healthy term infants tested on day four post normal pregnancy and spontaneous vaginal delivery
- Infants who had a history of perinatal distress but had no gross neurological signs
- Infants and children with congenital/acquired central nervous system lesions
- Children with treated metabolic disorders
- Few adult patients with degenerative disorders

Wolff defined non-nutritive sucking as any repetitive mouthing activity on a blind nipple other than biting. It was recorded from a commercial pacifier connected to a pressure transducer and visually displayed by a DC polygraph writer.

The parameters selected for analysis were based on changes in positive pressure as the lips and tongue alternately compressed and released the air in the rubber bulb. Therefore the final tabulations in this study do not account for all the important elements of sucking e.g. intra-oral negative pressure, sucking amplitude.

Nutritive sucking was defined as any repetitive mouthing on a nursing nipple associated with negative intra-oral pressure sufficient to deliver a potable liquid (e.g. milk, 5% glucose solution) from that nipple. Nutritive sucking was recorded in the same way as non-nutritive sucking, except that the pressure changes were recorded from a modified nursing nipple which would deliver fluid by a thin ethylene tube through its tip at the same time as it measured changes in the bulb of the nipple.

Four parameters were measured:

- Rate = frequency sucks per sec
- Stability of rhythm which was determined by calculating the variance in mean rate per second per burst per 10 second episode
- Characteristic alteration of bursts of mouthing and rest periods during non-nutritive sucking. The end of a burst was that segment of recording when the polygraph writer remained in the basement like position for more than one second.
- Rapid tongue and jaw tremors or "Q waves" appeared in the sucking records at a rate of 6-10/sec. As sick infants had more

tremors these were counted for the first 20 bursts of sucking for each infant.

From his results Wolff drew the following conclusions;
Normal infants suck in two distinct rhythms:

- A non-nutritive mode which is characteristically segmented into alternating bursts of sucking and rest periods, which has a basic frequency in the range 2 sucks per second, and which can be elicited in all arousal states except sleep and great excitement
- A nutritive mode, which usually depends on a flow of milk from the nipple, is organised as a continuous sequence of sucks, and has a basic frequency of about one suck per second.

He demonstrated that in the course of development, these patterns undergo some quantitative but no qualitative changes.

The non-nutritive sucking pattern of infants who had suffered various kinds of perinatal stress and showed no neurological signs differed from the normal pattern in one or more parameters. These differences were statistically significant. Yet, infants with major brain malformations showed perfectly normal sucking patterns in some instances.

In 1969 Gryboski and colleagues from Yale University developed the work of Wolff by looking at the polygraph recordings of premature infants (Gryboski, JD, 1969). The determination of suck-swallow patterns and oesophageal motility were performed on 40 premature infants between 1,700 and 2,500 gm birth weight. After, initial mouthing, two types of suck-swallow patterns were noted. The first "the immature suck-swallow pattern" consisted of a rate of 1 to 1.5 sucks per minute and consisted of

short sucking bursts preceded or followed by swallows. The second "the mature suck-swallow pattern" was characterized by bursts of over 30 seconds, and a rate of 2 per second. Swallows occurred frequently during sucking bursts. The smallest premature infants had poor peristalsis in the body of the oesophagus and did not attain a "mature suck-swallow pattern" until after peristalsis had become propagative. It was postulated in this article that the "immature suck-swallow pattern" prevents the delivery of a large amount of fluid, which could not be handled by an oesophagus, which has not yet developed the ability for adequate peristalsis.

There was a paucity of research in the 1970's in relation to infant sucking and indeed most of the work in the 1980's was in relation to swallowing. Bosma and colleagues looked at the postnatal ontogeny of performances of the larynx, pharynx and mouth highlighting how the infant anatomy in the region differs to the adult (Bosma JF, 1969, Gewodb IH, 2001). Throughout infancy and childhood, the senses of the pharynx, larynx and mouth guide their immediate actions and also provide the background, or substrate, for the further neurological development of these organs.

In 1996 Ramsay and Gisel (Ramsay M; Gisel EG, 1996) described a sucking apparatus- Whitney strain gauge (Parks Medical Electronics, Oregon, USA). Briefly, the sucking unit consisted of a pressure sensor device (strain gauge) and a portable computerized acquisition unit with a built-in plethysmograph, AC amplifier, and a video screen to obtain measurements of sucking frequency and duration. The strain gauge was placed under the infant's chin and secured with a tape over the infant's cheekbone. The AC amplifier provided a cyclical tracing as the infant lowered and raised the jaw during a sucking motion and did not interfere with feeding mode. To identify a sucking motion the gauge had to stretch

beyond 0.6% of its basement stretch during a jaw excursion. All polygraph tracings were analysed for the length of sucking bursts in seconds (sum of sucks where the amplitude of each suck was beyond 0.6% stretch on the polygraph) and time spent in sucking (sum of all sucking bursts). The time spent sucking in the first four minutes of recordings was expressed as a percentage.

In 2002 Ramsay and colleagues from Montreal Children's Hospital published an article using this technology on a large series of infants (Ramsay M et al, 2002). This prospective study examined the relation of neonatal sucking to later feeding, postnatal growth, maternal postnatal depression and feeding practices. Healthy infants of at least 37 weeks gestational age were recruited. At one week of age a strain gauge device was attached to the infant's cheek (as outlined in Ramsay's previous article) to identify sucking efficiency. Two hundred and two infants (100 males, 102 females; mean age 39.6 weeks, SD 1.1 weeks) with efficient sucking and two hundred and seven infants (101 males, 106 females; mean gestational age 39.4 weeks, SD 1.2 weeks) with inefficient sucking were identified. At one week inefficient sucking was defined as: duration of the initial sucking burst less than 30 seconds and less than 60% of time spent sucking in the first four minutes. At two months inefficient sucking was defined as duration of the initial sucking burst less than 60 seconds and less than 80% of time spent in sucking in the first 4 minutes. These cut-off points were based on studies by Dubignon and Cooper, Lucas and colleagues and the aforementioned pilot study by Ramsay and colleagues (Dubignon J, Cooper D, 1980; Lucas A et al, 1981; Ramsay M, Gisel EG, 1996). Borderline sucking was defined by the presence of only one of the above two conditions. They found in this study that inefficient neonatal sucking did not predict postnatal growth, later feeding difficulties, or maternal feeding practices. Maternal depression did not affect feeding

practices, infant feeding abilities, or growth suggesting that the importance of maternal postpartum depression in association with feeding problems may be less than previously presumed.

CHAPTER 6

Heart Rate Variability (HRV)

6.1   Background

Although fetal heart tones were first heard in the 1750s, the link between a reduction in the fetal heart rate (FHR) and stillbirth was not made before the beginning of the 19th century (Kergaredec, 1822). In 1833 the nature of meconium was speculated on and by the 1840s fetal auscultation was introduced as a means to establish fetal viability.

The end of the 1840s reported the first forceps deliveries for abnormal FHR. In 1876 the relationship between late decelerations and fetal death was acknowledged and in 1893 the first FHR criteria for fetal distress and rules for intermittent auscultation (IA) were laid down by Von Winkel (Schifrin and Suzuki, 1973). It is of note that 100 years later these have hardly changed and are still applicable today.

In 1906, only five years after Einthoven demonstrated the first electrocardiogram (ECG) in an adult, Cremer obtained a foetal ECG using abdominal and vaginal electrodes, which were attached to a simple string galvanometer (Cremer, 1906).

However it was not until after the introduction of the foetal scalp electrode in the early 1960s that difficulties in signal acquisition were overcome and improvements in signal processing techniques led to the introduction of foetal electrocardiogram (FECG) for intrapartum surveillance (Hon, 1963a). Continuous monitoring of the FHR by calculating the distance between the R peaks of the FECG became possible and early reports claimed the potential to reduce stillbirths with this form of foetal

surveillance (Hon 1963b; Hon and Lee, 1963; Hammacher, 1968). By the end of the 1960s, advances in doppler ultrasound technology provided a non-invasive trans-abdominal alternative of continuous FHR monitoring to the fetal scalp electrode.

6.2   Effect of Hypoxemia on the Heart

ST segment waveform changes occur during episodes of myocardial hypoxemia in adults and extrapolation of these changes to the hypoxemic fetus forms the background of ST waveform studies. The results of a number of controlled animal experiments suggest a relationship between changes in the T/QRS ration and deteriorating acid-base balance (Pardi et al, 1971; Rosen et al, 1976; Grenne et al, 1982; Rosen et al, 1984). However the largest animal study reported to date, comprising some 47 chronically instrumented lambs, which were subject to severe hypoxemia, did not reveal a significant correlation between the T/QRS ratio and fetal biochemical status (De Hann et al, 1995). Normoxemic fetuses, healthy children and exercising adults display an inverse relationship between the PR interval and FHR (Waterdog and Loogna, 1977; Murray, 1986; Donnerstein et al, 1990). In fetuses under hypoxemic circumstances, however, this relationship has been seen to reverse (Murray, 1986, 1992). An explanation for this changing PR-FHR relationship during fetal compromise is the different sensitivities of the sino-atrial (SA) node and the atrio-ventricular (AV) node to hypoxia. Parasympathetic stimuli causing FHR decelerations are unlikely to be responsible for a shortening of the PR interval as this is not how the AV node responds to such an autonomic nervous system activity.

Under these conditions it is more likely that the FHR falls as a result of hypoxia rather than parasympathetic activity, and that the increase in catecholamine levels associated with hypoxic stress results in the

shortening of the PR interval (Myers, 1972; Murray, 1992). Marked hypoxia slows the FHR due to the direct effect of oxygen on the oxygen-sensitive calcium channels in the SA node, reducing its sensitivity to adrenaline. The calcium channels in the AV node are relatively insensitive to hypoxia compared to the SA node. They are not affected directly and catecholamines will continue to shorten the PR interval. As a result the PR interval-FHR relationship will change from negative to positive. If sustained for longer than 20 minutes this positive relationship is found to be associated with acidemia at birth and in animal experiments it was seen that this changing relationship occurred simultaneous to the accumulation of lactate in the fetal circulation at a rate of at least 5mmol/L per 30 minutes (Murray, 1992). This changing relationship with increasing biochemical deterioration was confirmed in an analysis on experiments of 20 chronically instrumented sheep (Van Wijngarden et al, 1996a). This strongly supports the direct role of oxygen as a mediator in cardiac conduction and the potential of the PR time-interval-FHR relationship in fetal monitoring.

6.3 The Normal CTG

The Degree of Hypoxia and the Type of CTG Changes:

There are two main components of FHR patterns: baseline changes and periodic changes. Baseline changes are evaluated over ten-minute periods and changes in the rate which persist for more than ten minutes are considered to represent a new baseline. Abnormally high baselines are called tachycardia (>160bpm) and abnormally low rates bradycardia (<100 bpm). Periodic FHR changes are classified primarily on the basis of waveform and secondarily on the timing relationship between the beginning of a uterine contraction and the onset of the FHR change; they may be accelerations or decelerations. Most accelerations are considered

to indicate fetal well-being although occasionally they may co-exist with decelerations as "overshoots", in which case they are an ominous sign.

Three broad types of deceleration are defined by the shape and by their relationship to uterine contractions. They have been considered to have separate aetiologies but this is certainly an oversimplification.

6.3.1 Early decelerations

Early decelerations have uniform shapes and are so called because the onset of the decrease in FHR occurs simultaneously with the onset of contractions. These can be induced by compression of the fetal head, an effect which is thought to be mediated by the vagus nerve because it is blocked by atropine. Early decelerations are thought to be innocuous.

6.3.2 Late decelerations

Late decelerations also have a uniform shape and are so called because the nadir of the decrease in FHR occurs after the peak of the contraction. Late deceleration is believed to represent a sign of decreased fetal oxygenation resulting from uteroplacental insufficiency. It is thought that initially they reflect vagal stimulation secondary to mild hypoxia. When acidemia develops the mechanism of late deceleration appears to be primarily as a result of direct myocardial depression.

6.3.3 Variable decelerations

Variable decelerations are so called because they are of variable shape and have a variable relationship to uterine contractions. They are thought to be due to umbilical cord compression. Umbilical artery occlusion leads to sudden foetal hypertension and the resultant baroreceptor stimulation causes a reflex vagal FHR deceleration

The third major component of FHR trace patterns is variability. The time interval between successive heartbeats is normally uniform. This 'beat-to-beat' variability is called 'short-term' variability and is normally 2-3 bpm. Long-term fluctuations in FHR with a cycle of 3 to 5 bpm have an amplitude which is normally 5-20bpm. 'Long-term' variability below 5 bpm is considered to be abnormal.

Variability appears to reflect changes in the balance between the sympathetic nervous system that increases the FHR and the parasympathetic nervous system, which lowers the FHR. The earliest effect of hypoxia appears to be an increased variability possibly due to chemoreceptor activity. As hypoxia becomes more severe FHR becomes less variable possibly due to central depression of the autonomic nervous system by fetal endorphins (Goodlin, 1981).

6.4 The Relationship between Hypoxia and the CTG

The development of the internal scalp electrode led to a rapid growth in research into the relationship between FHR changes and events during labour. Hon and his co-workers in the USA and, independently, Caldeyro-Barcia in Uruguay reported various FHR changes that they related to 'fetal distress'(Caldeyro-Barcia R. al, 1964). Although tachycardia and bradycardia were classical signs of 'fetal distress' Hon (1959) distinguished between constant or 'baseline' bradycardia which were almost invariably associated with good foetal outcome and bradycardias which represented a change in rate from a previously higher level (Hon, 1959). He also described late foetal heart rate decelerations, which he thought were due to utero-placental insufficiency and variable decelerations which he ascribed to umbilical cord compression. Caldeyro-Barcia described similar changes (though he called them type II and type III decelerations respectively), and Hammacher related loss of fetal heart

rate variability to fetal distress. A common nomenclature was agreed following meetings between the various groups of investigators in 1971 and 1972.

6.5 Heart Rate Variability (HRV)

Clinical relevance of heart rate variability was first appreciated in 1965, when Hon and Lee noted that fetal distress was preceded by alterations in interbeat intervals, before any appreciable change occurred in heart rate itself (Hon EH, 1965). Twenty years ago Sayers (Sayers BM, 1973) and others (Hirsh, 1981; Lucask, 1973; Penaz, 1968) centred their research on the existence of physiological rhythms in the beat-to-beat heart rate.

In the 1970's Ewing et al (Ewing, 1985) devised a number of simple bedside tests of short-term RR differences to detect autonomic neuropathy in diabetic patients. Wolff et al first showed decreased heart rate variability is associated with higher post infarction mortality in 1977 (Wolf MM, 1978). In 1981 Akselrod et al (Akselrod, 1981) introduced power spectral analysis of heart rate fluctuations to quantitatively evaluate beat-to-beat cardiovascular control.

These frequency domain analyses contributed to the understanding of autonomic background of RR interval fluctuations in heart rate record (Pomeranz M, 1985). The clinical importance of heart rate variability became appreciated in the late 1980's when it was confirmed that heart rate variability is a strong independent predictor of mortality after an acute myocardial infarction (Bigger, 1992; Kleiger, 1987; Malik 1989).

6.6 Clinical Application and Interpretation of HRV

In 1996 a joint task force between the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, published a

special report (Malik M, 1996), highlighting the different mathematical and statistical methods that may be used for calculating heart rate variability (HRV) and their different clinical applications and limitations.

6.6.1 Time domain measurements of HRV

In these methods, either the heart rate at any point in time or the intervals between successive normal complexes are determined. In a continuous ECG recording, each QRS complex is detected and the so-called normal to normal (NN) intervals (that is, all intervals between adjacent QRS complexes resulting from sinus node depolarisations) or the instantaneous heart rate is determined.

Simple time domain variables that can be calculated include the mean NN interval, the mean heart rate, the difference between the longest and shortest NN interval, and the difference between night and day heart rate. Other time domain measurements that can be used are variations in instantaneous heart rate secondary to respiration, head tilt, phenylephrine. These differences can be described in either difference in heart rate or cycle length.

A: Statistical Methods

I   Those derived from direct measurements of the NN intervals or instantaneous heart rate.

II   Those derived from the differences between NN intervals.

SDNN = the standard deviation of the NN interval.

Variance = total power of spectral analysis.

SDNN reflects all the cyclic components responsible for variability in the period of recording. In many studies SDNN is calculated over a twenty-four hour period and thus encompasses short-term high frequency

variations as well as the lowest frequency components seen in twenty-four hours. As the period of monitoring decreases, SDNN estimates shorter and shorter cycle lengths. It should also be noted that the total variance of HRV increases with the length of analysed recording. In practice it is inappropriate to compare SDNN measures obtained from different durations. On the contrary, durations of the recordings used to determine SDNN values (and similarly other HRV measures) should be standardized. Short-term 5-minute recordings and nominal 24-hour long-term recordings appear to be appropriate options.

B: Geometric Methods
I   Sample density distribution of differences between adjacent NN
        intervals.
II   Lorenz plot of NN/RR intervals.

A simple formula is then used that judges the variability on the basis of the geometric and/or graphics properties of the resulting pattern. Three general approaches are used in geometric methods: A basic measurement of the geometric patterns converted into the measure of HRV; the geometric pattern is interpolated by a mathematically defined shape and then the parameters of this mathematical shape are used; the geometric shape is classified into several pattern-based categories that represent different classes of HRV.

Most geometric methods require the RR (or NN) interval sequence to be measured on or converted to a discrete scale that is not too fine or too coarse and permits the construction of smoothed histograms. The major advantage of the geometric methods lies in their relative insensitivity to the analytical quality of the series of NN intervals. Distinction should be made between measures derived from direct measurements of NN

intervals or instantaneous heart rate and from the differences between NN intervals. It is inappropriate to compare time domain measures, especially those expressing overall HRV, obtained from recordings of different durations.

6.6.2 Frequency domain methods

Various spectral methods for the analysis of the ECG have been applied since the late 1960's. Power spectral density (PSD) analysis provides the basic information of how power (variance) distributes as a function of frequency.

Independent of the method used only an estimate of the true PSD of the signal can be obtained by proper mathematical algorithms.

Methods for the calculation of PSD may be generally classified as nonparametric and parametric. In most instances, both methods provide comparable results. The advantages of the non-parametric methods are: The simplicity of the algorithm used (fast Fourier transformation [FTT]); the high processing speed. While the advantages of the parametric methods are: (a) Smoother spectral components that can be distinguished independent of preselected frequency bands; (b) Easy post-processing of the spectrum with an automatic calculation of low- and high-frequency power components with an easy identification of the central frequency of each component; (c) an accurate estimation of PSD even on small number of samples.

Spectral components can be either short-term or long-term recordings:

Short-term recordings: Three main spectral components are distinguished in a spectrum calculated from short-term recordings of 2 to 5 minutes. Very low frequency (VLF), high frequency (HF) and low frequency (LF)

components. The distribution of the power and the central frequency of the HF and LF are not fixed but may vary in relation to changes in autonomic modulations of heart period. VLF assessed from short-term recordings (</=5mins) is a dubious measure and should be avoided when the PSD of short-term ECGs is interpreted.

Long-term recordings: Spectral analysis also may be used to analyse the sequence of NN intervals of the entire 24-hour period. The result then includes an ultra low frequency (ULF) component as well as, VLF, LF and HF. The slope of the 24-hour spectrum also can be assessed on a log-log scale by linear fitting the spectral values.

In the analysis of stationary short-term recordings, more experience and theoretical knowledge exist on physiological interpretation of the frequency domain measures compared with the time domain measures derived from the same recordings.

On the contrary, many time and frequency domain variables measured over the entire 24-hour period are strongly correlated with each other. These strong correlations exist because of both mathematical and physiological relationships. In addition, the physiological interpretation of the spectral components calculated over 24 hours is difficult. Thus, unless special investigations are performed that use the 24-hour HRV signal to extract information other than the usual frequency components, the results of frequency-domain analysis are equivalent to those of the time domain analysis, which is easier to perform.

6.7 How Beat To Beat Variations (CTG) Differ From HRV

As explained earlier CTG looks at the beat-to-beat variations in the FHR and attempts to correlate them with uterine contractions during labour. It

is limited by the inter and intra observer variability and is at best a subjective science. Few studies have been mounted to assess the 'repeatability' (intra- and inter- observer variation) of trace interpretation. In 1982 Cohen et al examined the extent of agreement and disagreement in interpretation and clinical response to intra-partum traces. Twelve obstetricians recognised in the USA for their scientific and clinical contributions to EFM were interviewed. A description of 14 FR patterns was supplied, each of which would generally be considered to be 'abnormal'. The obstetricians were asked to classify the traces into three levels of severity: Ominous; Non-reassuring; and Innocuous. They were then asked what clinical action they would take if conservative treatment failed, firstly if foetal blood acid-base was not available and secondly if it was available. In the initial assessment of the traces there was near perfect agreement over five traces, fair agreement over a further five, but marked disagreement over four others. Faced with the choice of continuous monitoring or immediate delivery the obstetricians agreed closely in four cases, agreed moderately in eight and disagreed markedly in two.

In this study by Cohen and his colleagues, descriptions of trace patterns were supplied to the 14 obstetricians; they were not asked to interpret and categorise actual EFM traces. Had this been done it is likely that it would have increased further the variation between clinicians. Trace interpretation can be difficult and it is surprising that this aspect of EFM has been the focus of so little formal research.

HRV on the other hand is objective and calculated by software packages either using time domain or frequency domain methods as described earlier. It formally calculates the RR interval and measures its variability giving answers in time (seconds). It has been shown in the adult literature to be a very good predictor of long-term outcome post myocardial

infarction. Its main focus in children has been in the attempt to predict those infants most likely to succumb to sudden infant death (SIDS) (Matthews TG, 1992). Recent research has demonstrated that it is a good predictor for the development of neonatal sepsis in premature infants (Rosen H et al, 2000; Griffin MP et al, 2003).

HRV is limited by the lack of consistency in the methods chosen to calculate it making it almost impossible to compare results form other studies and to formalise normal values.

6.8 The Predictive Value of CTG and HRV

Following the Dublin Randomised Trial it was demonstrated the EFM compared to intermittent auscultation (IA) significantly reduced the number of babies who went on to develop neonatal seizures (Mac Donald D et al, 1986). Long-term data is not so reassuring. A Cochrane database analysis of all EFM studies as well as work carried out by Karin Nelson in the USA have shown beyond doubt that while specific abnormal findings on electronic monitoring of the fetal heart were associated with an increased risk of cerebral palsy, the false positive rate was extremely high (Nelson K et al, 1996, 2003; Thacker SB et al, 2001). As caesarean section is often performed when such abnormalities are noted and is associated with risk to the mother, the 'relentless rise ' in caesarean section as yet does not appear to be reducing the overall neonatal morbidity (Murphy JFA, 2003).

HRV has been demonstrated to be predictive in terms of neonatal sepsis and SIDS. In this study I chose HRV as the third parameter I measured for three reasons. Firstly asphyxia when severe is said to be multi-organ with creatinine kinase (CK) often used in initial assessment of newborn babies thought to be suffering from NE. Secondly, if CTG is the antenatal

monitoring used in an attempt to detect fetal distress then it would seem that HRV is a natural post-natal continuum of same. Thirdly, it is derived by an objective mathematical calculation that eliminates observer variability.

6.9 Would the HRV Correlate with the Acidemia, the EEG or the Neurological Parameters

In a study by Rosen et al (Rosen H et al, 2000), it was demonstrated that mean heart rate was significantly greater in awake infants than in sleeping infants. I postulated at the start of my research that if any HRV abnormalities were to be found they would probably correlate best with degree of acidemia because of the direct effect of hypoxemia on the heart and EEG recording especially during the quiet sleep (QS) portion of the recording.

CHAPTER 7

Patients and Methods

7.1 Patient inclusion and exclusion criteria

Setting:

The National Maternity Hospital, Holles Street, Dublin 2.

Ethics and Consent:

Ethical permission was obtained from the ethics committee at The
National Maternity Hospital in November 2000. Written informed
parental consent was obtained for each infant enrolled.

Patients:

A cohort of term infants (> 37 weeks gestation) were recruited who met
one of the following criteria.

Inclusion criteria:

- Emergency section,
- Assisted delivery (forceps/ventouse),
- Presence of meconium stained liquor
- Low pH (≤ 7.25) on fetal blood sampling taken during labour.

These infants had a cord pH sample taken at the time of delivery. They
were then subdivided based on this pH value. Exposure to severe acidosis
was deemed to be those infants with a cord pH value ≤ 7.0. The
controls/non-exposed were those infants with an arterial cord pH value

7.01- 7.25. As spontaneous vaginal delivery (SVD) and elective Caesarean section were considered low risk deliveries, those infants were excluded.

A trained neonatologist clinically examined all infants. They were deemed to be either clinically normal or to have varying degrees of encephalopathy. The degree of encephalopathy was recorded using the Sarnat scoring system (Sarnat, 1976). This divides neonatal encephalopathy (NE) into three stages (Table 7.1).

Statistics:

A sample size of 75 was prospectively calculated. Based on previous data from The National Maternity Hospital (table 1.1) it was estimated that this would demonstrate a 30% difference between infants with severe acidosis (cord pH ≤ 7.0) and infants with mild to moderate acidosis (cord pH 7.01-7.25). This sample size would allow for a type II error. Confidence intervals were set at 95%.

I recruited all infants with a cord pH value ≤ 7.0 and all infants who had clinical signs of encephalopathy irrespective of cord pH values. For each infant with a pH value ≤ 7.0 and who had no signs of encephalopathy, I recruited the next three consecutive infants who met the study criteria, were clinically normal and had a pH value 7.01-7.25 as controls.

7.2   Characteristics of study population: Infants and Mothers.

During the study period (July 2001-June 2002) 90 patients were recruited. 51 (57%) of the infants were male. Mean gestation was 40wks and 1.4 days (+/- 8.6 days). The mean birth weight of the entire group was 3.52kg (+/- 0.8). 25 infants had a cord pH value ≤ 7.0 with 65 having a pH value

7.01- 7.25. 22 infants had clinical evidence of encephalopathy with 68 appearing to be clinically normal. 50 (55.7%) of the mothers were primiparous (i.e. this was their first child) compared to 40 (44.4%) who were multiparous.

36 were delivered by caesarean section. 26 (72%) of these were male. Mean gestational age was 40 weeks (+/- 9 days). 7 had no labour at all; of the 29 whose mothers did labour the mean length of the first stage (1 to 10 cm dilatation) was 7.29 hours (+/- 3.05). 9 of these proceeded to caesarean section because of failure to advance i.e. arrest of first stage. The mean birth weight in the section group was 3.5kg (+/- 0.56). 22 (57.8%) of the mothers in the caesarean section group were primiparous.

27 infants were delivered by spontaneous vaginal delivery, with a mean birth weight of 3.65kg (+/-0.47). 15 (55.5%) of these were girls. The mean gestational age in this group was 40 weeks and 1.4 days (+/- 8 days). The mean length of the first stage of labour in this group was 5.45 hours (+/-3.28). 15 (55.5%) of this group were primiparous.

25 infants were delivered by assisted delivery (15 ventouse delivery, 10 forceps). 13 of these were boys. The mean gestational age was 40 weeks and 3 days (+/- 8 days). The mean birth weight in the ventouse group was 3.55kg (+/- 0.56) compared to 3.74kg (+/- 0.53) in the forceps group. The mean length of the first stage of labour in the assisted delivery group was 5.85 hours (+/- 2.5), with little difference between the ventouse (5.85 hours) and forceps group (5.8 hours). 14 (56%) of the assisted delivery group were primiparous.

2 infants were born by breech delivery, one male infant and one female infant 38 and 39 weeks gestation respectively, with a mean birth weight of

2.78kg(+/0.39). The mean length of the first stage of labour was 6.7 hours (+/- 1.5hrs.). One of the mothers in this group was primiparous.

I then compared the infant characteristics of those with and without neonatal encephalopathy. There were 22 infants who showed signs of encephalopathy (Sarnat I-III) and 68 who were clinically normal.

Looking first at the encephalopathic group, 14 (64%) were male, the mean gestation was 40 weeks and one day (+/- 9 days), the mean birth weight was 3.415kg (+/-0.91) and 14 (64%) of their mothers in the were primiparous. 8 (36%) of these infants had a cord pH value < 7.0. The mean length of the first stage of labour was 5 hours and 47 minutes (+/- 4hours).

In the non-encephalopathic group (n=68) the characteristics were as follows. 35 (52%) were male, the mean gestation was 40 weeks and 3 days (+/- 8 days), the mean birth weight was 3.418kg (+/- 0.85) and 30 (44%) of the mothers were primiparous. 17 (25%) of these infants had a cord pH value ≤ 7.0. The mean length of the first stage was 5 hours 6 minutes (+/- 3 hours).

7.3   Methods

7.3.1 Cord pH measurements

Infants had arterial and venous cord blood gases taken and analysed within five minutes of delivery. The National Maternity Hospital has been routinely performing cord blood pH analysis in high-risk deliveries since 1976 following the work of Saling et al in the late 1960's (Saling, 1962). Following two large randomised controlled trials in the hospital, midwives are very competent in this procedure and it is routine for all high-risk

deliveries to have cord blood gases taken (1,000 per annum) (MacDonald D, 1985, Impey L, 2003).

Using monovette 2ml lithium heparin syringes with 21 gauge needles, having double clamped the cord, samples were taken from the umbilical artery and an umbilical vein. Samples were analysed by a "Bayer" blood gas analyser, which provides a pH, pO_2, pCO_2, bicarbonate and base excess value. Infants were divided into cases (cord pH $\leq$ 7.0) and controls (cord pH 7.01-7.25) based on the umbilical arterial cord pH values

7.3.2 EEG analysis

Each infant recruited had a 30 lead digital EEG with video within 48 hours of birth recorded for one hour. EEGs were assessed in the following manner.

- Length of time in each of the three states was measured and expressed as a percentage of the total one-hour recording.
- A random 10 second epoch of each of the three sleep states was selected for each infant i.e. 10 second epoch of quiet sleep (QS), active sleep (AS) and the awake state (AW). For each 10-second epoch the following analysis was carried out.

  I Number of sharp waves

  II Maximum and minimum amplitude (Micro volts)

  III Background frequency (Hertz)

- For quiet sleep the following analysis was also performed.

  I Length of interburst interval (seconds) i.e. the low amplitude portion of quiet sleep. Normally 3-6 seconds.

  II Whether interhemispheric synchrony was present or not.

To remove bias an independent observer also analysed each EEG blinded to both the infant's clinical status and pH value. There was a 93% concurrence with analysis and when a difference in values was present those submitted by the independent observer were used in the final analysis.

7.3.3 Suck reflex integrity

The sucking response was measured using a closed pressure circuit, (see Fig. 1). This consisted of a sterile disposable teat (A) attached to an intersurgical 22mm straight connector (22M/22F/7.6mm port) (code: 1964) (B), attached to an intersurgical 7.6mm female leur fitting (non-removable) (Code: 2710) (C), which was in continuity with an umbilical arterial catheter (D), this was attached to an invasive blood pressure cable (P/N MX98002) (E), which was linked with an Agilent (Philips medical) CMS patient monitor (F). This system was capable of measuring pressures from 0 to –30mmHg.

All data were then stored on datan GmBH dataplore software for analysis. In each case the non-nutritive sucking pattern was analysed within forty-eight hours of delivery. The sterile disposable teat was placed in the infant's mouth and the sucking response recorded. The measurements were recorded for a period of 5 minutes when the baby was fully awake and pre-feed.

The following parameters were measured:
- The overall suck frequency (i.e. total number of strokes in 5 minute period),
- The suck frequency in three pressure bands. 0 to –10mmHg, -10 to –20mmHg and –20 to –30mmHg,

- The duration of the intersuck interval (secs) i.e. the length of time that no sucking occurred (0mmHg), during the 5-minute recording.

In the case of infants who reached a negative pressure of −30mmHg I measured the maximum duration (secs), that suck was maintained at −30mmHg

7.3.4 Heart Rate Variability

Each infant recruited into the study had a continuous electrocardiogram (ECG) recording for one hour within forty-eight hours of delivery. This was recorded simultaneously with the EEG recording. The ECG was recorded on an Agilent (Philips medical) CMS patient monitor. All data were then stored on datan GmBH dataplore software for analysis. Initially three standard ECG leads were used for the recording. However these recordings had a lot of movement artefact, which made subsequent analysis difficult. Through trial and error I found that using EEG electrodes on the chest and naval gave a better quality ECG trace. Therefore from infant fifteen on EEG electrodes were employed for the ECG recording.

As the literature suggests that either 24 hour or 5-minute recordings are the most accurate, I selected a 5-minute epoch of the ECG during quiet sleep (as confirmed by the EEG), as the section for analysis (Malik M, 1996). Each 5-minute recording was analysed by the dataplore software using a geometric method of analysis. This allowed me to calculate the mean, median, standard deviation and variance of the heart rate variability over the 5 minute selected epoch in milliseconds.

Table 7.1   Sarnat scoring system for stages of Neonatal Encephalopathy (NE)

Signs	Stage 1	Stage 2	Stage 3
Level of consciousness	Hyperalert	Lethargic	Stuporous
Muscle tone	Normal	Hypotonic	Flaccid
Tendon reflexes	Hyperactive	Hyperactive	Absent
Moro reflex	Strong	Weak	Absent
Seizures	None	Common	De-Cerebration
EEG	Normal	Low voltage/ seizure activity	Burst suppression
Duration	< 24 hrs	24 hr to 14 days	Days to Weeks

Table 7.2a Neonatal Encephalopathy (NE): Patient characteristics in cases and controls.

Parameter	NE present (n=22)	No NE (n=68)	p value
No. (%) mothers who were primiparous	15 (68)	23 (33)	< 0.05
No. (%) mothers who smoked during pregnancy	3 (14)	22 (33)	NS
No. (%) mothers who drank alcohol during pregnancy	2 (9.0)	12 (17.7)	NS
Mean birth weight (kg)	3.4 (+/- 0.91)	3.4 (+/-0.85)	NS
Mean gestation (weeks)	40+1day(+/-9days)	40+2days(+/-8days)	NS
No. (%) cord pH ≤ 7.0	8 (36)	17 (27)	NS
No. (%) infants 1 min Apgar score of			
0-3	7 (32)	4 (4.4)	< 0.01
4-6	8 (36)	14 (20)	NS
7-10	7 (32)	50 (75)	< 0.01
No. (%) infants 5 min Apgar score of			
0-3	2 (9)	0 (0)	NS
4-6	11 (50)	0 (0)	< 0.01
7-10	9 (41)	68 (100)	< 0.01

Table 7.2b   Neonatal Encephalopathy (NE): Patient characteristics in cases and controls.

Parameter	NE (n=22) present	No NE (n=68)	p value
Mode of delivery			
No. (%)			
Vaginal	2 (9)	25 (37)	< 0.05
Ventouse	6 (27)	13 (19)	NS
Forceps	3 (13.6)	4 (6.6)	NS
C*. Section	11 (50)	24 (35)	NS
Breech	0 (0)	2 (4.4)	NS
Epidural No. (%)	10 (45.4)	50 (73)	< 0.05
ARM No. (%)	9 (41)	14 (20)	NS
Prostin No. (%)	6 (27)	6 (8.8)	NS
Oxytocin (%)	11 (50)	35 (51)	NS
Mean length of 1st stage of labour (hrs +/- SD)	5hrs 47mins (+/- 4hrs)	5hrs 6 mins (+/- 3hrs)	NS
Mean length of 2nd stage of labour (mins +/-SD)	48mins (+/-50)	72mins (+/-35)	< 0.01

*C denotes cesarean

Table 7.3a   Patient characteristics in cases with pH ≤ 7.0 and
cases with pH 7.01-7.25

Parameter	Cord pH value ≤ 7.0 (n=25)	Cord pH value 7.01-7.25 (n=65)	p value
No. (%) mothers who were primiparous	15 (60)	36 (55)	NS
No. (%) mothers who smoked during pregnancy	7 (28)	11 (17)	NS
No. (%) mothers who drank alcohol during pregnancy	4 (16)	7 (10.8)	NS
Epidural No. (%)	15 (60)	29 (44.6)	NS
Pethidine No. (%)	2 (9)	4 (6.2)	NS
ARM No. (%)	14 (56)	5 (7.8)	< 0.01
Prostin No. (%)	2 (9)	2 (3)	NS
Oxytocin No. (%)	7 (28)	12 (18.5)	NS
Mean length of 1st stage of labour (hours)	5 .5 (+/- 3.5)	4 .5 (+/- 3.2)	NS
Mean length of 2nd stage of labour (mins)	50 (+/-48)	83 (+/- 132)	NS

Table 7.3b   Patient characteristics in cases with pH ≤ 7.0 and
  cases with pH 7.01-7.25

Parameter	Cord pH value ≤ 7.0 (n=25)	Cord pH value 7.01-7.25 (n=65)	p value
No. (%) infants			
With 1 min Apgar score			
Of 0 - 3	5 (20)	8 (12.3)	NS
4 – 6	15 (60)	12 (18.5)	< 0.01
7 – 10	5 (20)	45 (69)	< 0.01
No. (%) infants			
With 5 min Apgar score			
Of 0 – 3	0 (0)	4 (6.2)	NS
4 – 6	14 (56)	5 (7.6)	< 0.01
7 – 10	11 (44)	56 (86.2)	< 0.01
Mean birth weight (kg)	3.52 (+/- 0.45)	3.58 (+/- 0.56)	NS
Mean gestation (weeks)	40 wks + 3 days (+/- 8 days)	40 wks + 1 day (+/- 9 days)	NS
Infant M: F ratio	2.5:1	1:1.4	< 0.05

Total number of term births

5,800

Term infants with cord pH ≤7.25

634

Infants cord pH ≤ 7.0   Infants cord pH 7.01-7.25

25   609

Infants with NE	Infants without NE	Infants with NE	Infants without NE
8	17	14	595
↓	↓	↓	↓
All had EEGs	All had EEGs	All had EEGs	Random sample 51 infants had EEGs
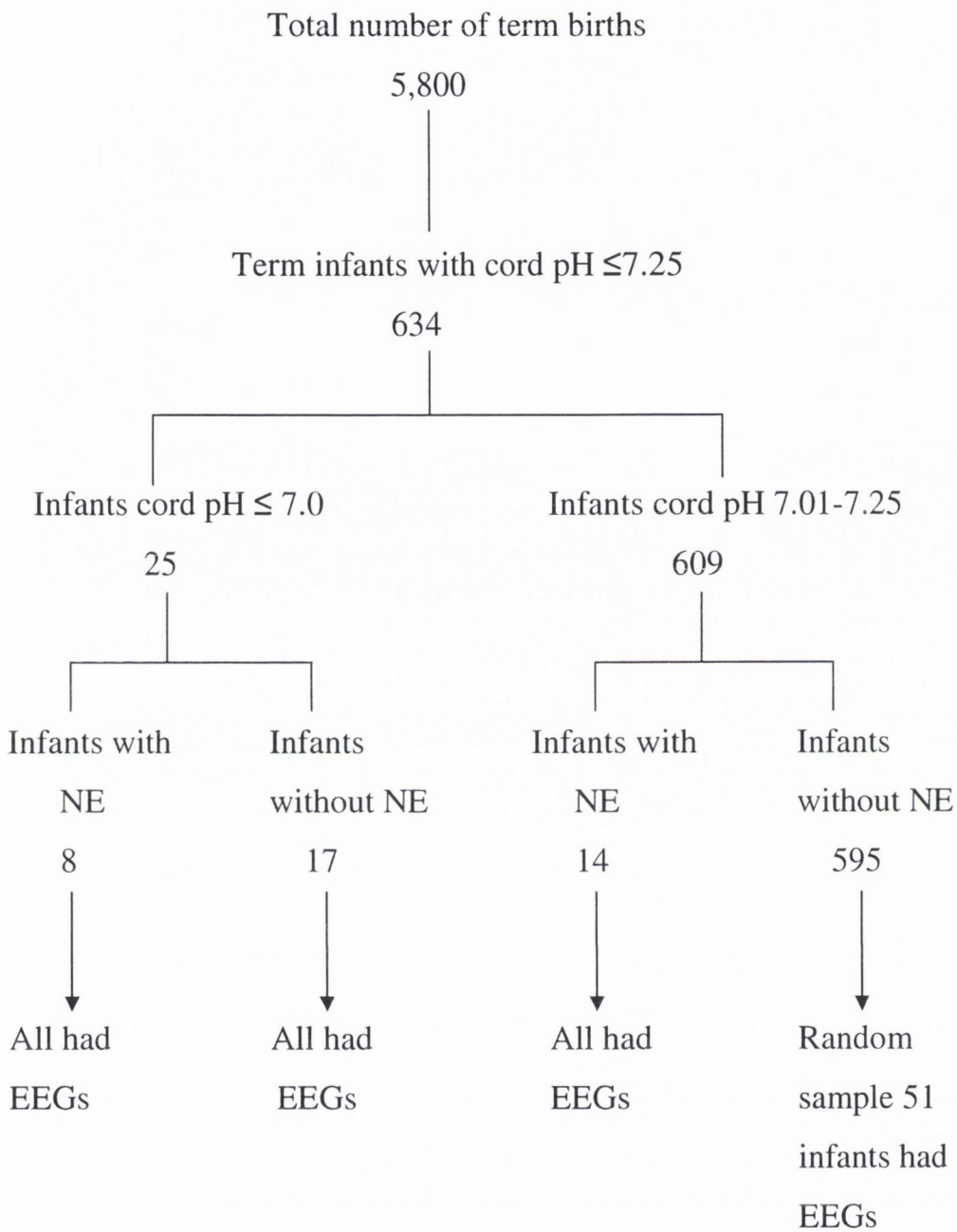
NE: Neonatal Encephalopathy

Fig 7.2   Inclusion criteria for the performance of EEGs in infants with low cord pH values.
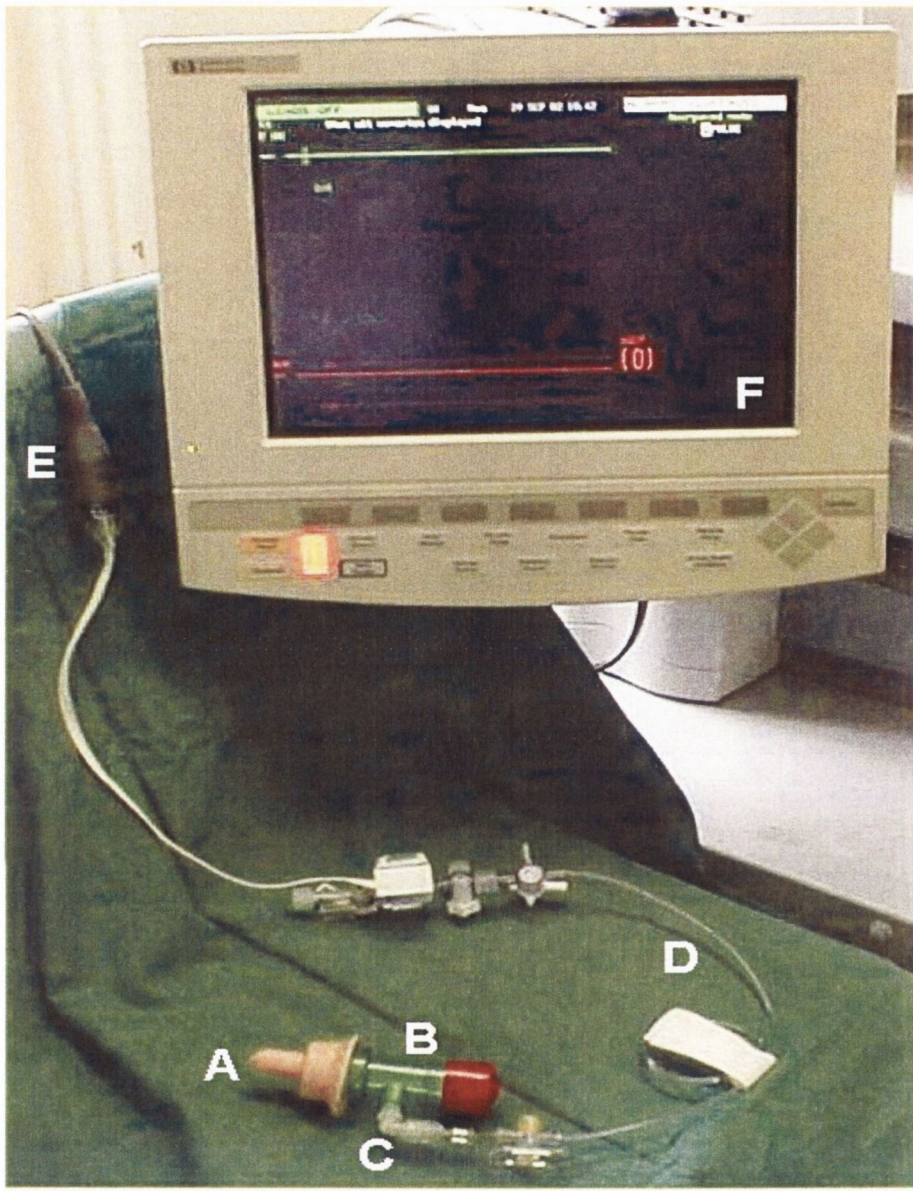
Fig 7.3   Infant Manometric Suck Apparatus

- Sterile disposable teat (A)
- Intersurgical 22mm straight connector (B)
- Intersurgical 7.6mm female leur fitting (C)
- Umbilical arterial catheter (D)
- Invasive blood pressure cable (E)
- Agilent patient monitor (F)

CHAPTER 8

Results

8.1 General Results

Fig 7.2 shows how the results have been analysed and presented. Analysis was based on an umbilical cord pH value of ≤ 7.0 or 7.01- 7.25. The three main subgroups, which I compared, were as follows:

- All infants with neonatal encephalopathy (NE) irrespective of their cord pH value.
- All babies born with a cord pH value of ≤ 7.0 irrespective of their clinical status.
- Random selection of babies who were clinically normal and had an arterial cord pH value 7.01- 7.25.

Between July 2001 and May 2002 634 babies were born who met the high risk study criteria and had an arterial cord pH value ≤ 7.25. Twenty-five of these infants had a cord pH ≤ 7.0 and 609 had a pH 7.01-7.25. Eight of the 25 infants (32%) with a cord pH ≤ 7.0 had clinical evidence of significant encephalopathy (Sarnat II/III), compared to 14 of the 609 infants (2.2%) with a cord pH between 7.01-7.25. This is highly statistically significant with a p value of 0.000002, an odds ratio (OR) of 20.5 and a relative risk (RR) of 16. This means that the risk of encephalopathy in high-risk deliveries increases 16 fold once the arterial cord pH value is ≤ 7.0 (Table 8.1).

8.2   Results of EEG analysis

The EEG data was examined and the findings compared between those
infants:

- According to a cord pH ≤ 7.0 and a cord pH 7.01-7.25.

- According to those with NE and those without NE.

- Infants with no NE according to cord pH ≤ 7.0 and cord pH 7.01

  7.25.

I examined the results of the detailed EEG analysis and compared

encephalopathic infants with a cord pH ≤ 7.0 to those infants with a cord

pH 7.01-7.25 (Table 8.2). The following three findings were significantly
different: Maximum amplitude per 10 second epoch of Quiet Sleep (QS)

which was greater in those with a cord pH ≤ 7.0 (65 compared to 28 micro

volts, p value = 0.002); Number of sharp waves per 10 second epoch of

QS were greater in those with a cord pH ≤ 7.0 (11 compared to 3.2, p

value = 0.009); The length of the interburst interval in QS which was

significantly longer in those with a cord pH ≤ 7.0 (30.6 compared to 13.1

seconds, p value = 0.012).

The EEGs of infants with cord pH ≤7.0 were then separately analysed

both for those with encephalopathy and those with no encephalopathy.
The same three parameters of EEG analysis were significantly different
between those with encephalopathy and those with no encephalopathy
(Table 8.3): Maximum amplitude per 10-second epoch of QS was
significantly greater in those infants with encephalopathy compared to

those with no encephalopathy, (65 versus 40 microvolts-p value = 0.009); Number of sharp waves per 10 second epoch of QS was significantly greater in those infants with encephalopathy compared to those infants with no encephalopathy (11 versus 3.3 sharp waves-p value = 0.009). Length of the interburst interval during QS was significantly longer in those infants with encephalopathy compared to those infants with no encephalopathy (30.6 seconds versus 4.6 seconds, p value = 0.007).

I then examined the EEG results of the subset of infants who had no clinical evidence of encephalopathy and compared the 17 babies with a cord pH ≤ 7.0 with the 51 randomly selected infants with a pH value between 7.01-7.25 (Table 8.4).

The length of the interburst interval was significantly longer in those infants with a cord pH ≤ 7.0, compared to those infants with a cord pH 7.01-7.25 (4.6 versus 3.6 seconds, p value = 0.005).

However, there was no significant difference between the maximum amplitude and number of sharp waves per 10-second epoch of quiet sleep, between these two subsets of infants.

8.3   Results of Sucking Integrity

As with the EEG analysis I compared infants based on their cord pH values and compared three subsets of infants and their sucking patterns:

- According to a cord pH ≤ 7.0 and a cord pH 7.01-7.25.

- According to those with NE and those without NE.

- Infants with no NE according to cord pH ≤ 7.0 and cord pH 7.01-7.25.

Sucking patterns differed greatly between those infants with encephalopathy and those with no encephalopathy. (Table 8.5). Firstly the total frequency of strokes was lower in those with encephalopathy (75.9 Vs 114.5). When one examines the breakdown of these strokes, there was a significant difference in the higher-negative category pressure band (-20 to –30mmHg). Infants with NE had a much lower number of strokes in this higher range compared to infants with no NE (29 Vs 73.4). When infants reached a negative pressure of –30mmHg, those with NE were much poorer at sustaining it there compared to those with no NE (0.12 Vs 56.6 secs). Infants with NE also had a much longer intersuck interval compared to those infants with no NE (37.9 Vs 14.5 secs).

Infants with a cord pH ≤ 7.0 irrespective of their clinical condition had a lower number of strokes over a 5-minute epoch compared to those infants with a cord pH 7.01-7.25 (70.1 Vs 119.2). There was a lower number of strokes in the higher negative category pressure band of –20 to –30mmHg in those infants with a cord pH ≤ 7.0 compared to those infants with cord pH 7.01-7.25 (27.4 Vs 47.6). There was a significant difference in the duration of the intersuck interval with infants having a cord pH ≤ 7.0 having a shorter interval than those infants with cord pH 7.01-7.25(26.9 Vs 43.37secs). There was little difference in the mean duration infants sustained their suck at –30mmHg between those with cord pH ≤ 7.0 and those with cord pH 7.01-7.25 (28.9 Vs 27.8 secs).

I examined the subset of infants with a cord pH value of ≤ 7.0 and divided them into those with neonatal encephalopathy (NE) and those with no NE. Infants with NE had a lower number of strokes compared to infants without NE (64.3 Vs 76.2) which was most marked in the higher-negative pressure category of –20 to –30mmHg (6.25 Vs 48.6). The duration of time infants with NE sustain their suck at –30mmHg was shorter compared to infants with no NE (0.06 Vs 57.7 secs). The length of the intersuck interval was longer for those infants with NE compared to those infants with no NE (40.12 Vs 14.45 secs).

I then looked at the sucking patterns of those infants with no NE and compared those infants with cord pH ≤ 7.0 and those with cord pH 7.01-7.25. There was no significant difference in the total frequency of strokes between those infants with cord pH ≤ 7.0 and those infants with cord pH 7.01-7.25 (76.2 Vs 96.9). When I performed sub-analysis there was no difference in the mean number of strokes sustained at the higher negative pressure category (-20 to –30mmHg) between those infants with cord pH ≤ 7.0 and those infants with cord pH 7.01-7.25 (48.6 Vs 58.1). There was however a significant difference in the mean length of time the suck was sustained at a negative pressure of –30mmHg over a 5-minute epoch, between those infants with cord pH ≤ 7.0 and those infants with cord pH 7.01-7.25 (57.7 seconds VS 136.7 seconds). The median duration infants sustained their suck at a pressure of –30mmHg over a 5-minute epoch, showed no difference between those infants with a cord pH ≤ 7.0 and those infants with cord pH 7.01-7.25 (21 seconds Vs 25 seconds). There was no significant difference in median duration of the intersuck interval

between those infants with cord pH ≤ 7.0 and those infants with cord pH 7.01-7.25 (13.2 seconds Vs 20 seconds).

8.4 Results of heart rate variability (HRV)

Heart rate variability (HRV) was calculated and compared between the following sets of infants:

- According to a cord pH ≤ 7.0 and a cord pH 7.01-7.25.

- According to those with NE and those without NE.

- Infants with no NE according to cord pH ≤ 7.0 and cord pH 7.01-7.25.

There were 16 infants with a cord pH ≤ 7.0 and 42 infants had a cord pH 7.01-7.25.

In infants with NE there was no difference in the HRV between those with cord pH ≤ 7.0 and those with cord pH 7.01-7.25 (490 Vs 498 millisecs), (Table 8.9).

In relation to those infants with cord pH ≤ 7.0 (Table 8.10), there was no significant difference in the mean HRV between those infants with neonatal encephalopathy (NE) and those infants with no NE (490 Vs 539 millisecs).

Among those infants with no NE, (Table 7.11) there was no difference in the HRV between those with cord pH ≤ 7.0 and those with cord pH 7.01-7.25.

Table 8.1   Rates of neonatal encephalopathy (Sarnat II/III) in infants with a
cord pH ≤ 7.0 compared, to those infants with cord pH 7.01 - 7.25

Cord pH	Total No. Infants	No.(%) Infants with NE*
≤7.0	25	8 (32)
7.01-7.25	609	14 (2.2)
Total	634	22 (3.4)

(p = 0.000002; OR = 20.49; RR = 16.)

*NE denotes Neonatal Encephalopathy

Table 8.2   EEG analysis in infants with *NE according to cord pH ≤ 7.0
and cord pH 7.01-7.25

Cord pH	No. of infants	Max. amp. Per 10 sec Epoch QS (microVlts)	No of sharp waves per 10 sec QS	Length of IBI QS (secs)
≤ 7.0	8	65	11	30.6
7.01-7.25	14	28	3.3	13.1
p value		<0.05	<0.05	<0.01

*NE denotes Neonatal Encephalopathy

Table 8.3   EEG Analysis of infants with a cord pH ≤ 7.0 according to those
wth *NE and those with no *NE

Clinical Status	No. of infants Cord pH ≤ 7.0	Max. amp. per 10 secs Epoch QS (mVlts)	No. of sharp waves per 10 sec epoch QS	Length of interburst interval QS (secs)
With NE*	8	65.0	11.0	30.6
No NE*	17	40.2	3.4	4.6
P value		<0.01	<0.01	<0.01

*NE denotes Neonatal Encephalopathy

Table 8.4   EEG analysis in infants with no *NE according to infants with cord pH ≤7.0 and cord pH 7.01-7.25

Cord pH	No. of infants	Max. amp. per 10 secs Epoch QS (mVlts)	No. of sharp waves per 10 sec epoch QS	Length of interburst interval QS (secs)
≤ 7.0	17	40.2	3.4	4.6
7.01 – 7.25	51	44.6	2.5	3.6
p value		NS	NS	<0.05

*NE denotes Neonatal Encephalopathy

Table 8.5   Suck pattern in infants with NE* and infants with no NE*

Parameter	NE*	No NE*	
	20 Infants	44 Infants	p value
Total frequency of strokes over 5 min epoch	75.9	114.54	<0.05
No. of strokes according to a negative pressure category			
0 to –10mmHg	36.8	32.1	NS
-10 to –20mmHg	10.1	9.0	NS
-20 to –30mmHg	29	73.35	<0.01
Maximum duration Suck sustained at a negative Pressure of			
-30mmHg (secs)	0.12	56.6	<0.05
Duration of intersuck interval (secs)	37.92	14.45	NS

*NE denotes Neonatal Encephalopathy

Table 8.6   Suck pattern in infants with cord pH ≤ 7.0 and infants with cord pH 7.01-7.25

Parameter	pH ≤ 7.0 17 infants	pH 7.01-7.25 47 infants	p value
Total number of strokes over 5 min epoch	70.1	119.2	<0.001
No. of strokes according to a negative pressure category			
0 to –10mmHg	32.5	40.5	<0.05
-10 to –20mmHg	10.2	31.1	<0.01
-20 to –30mmHg	27.4	47.6	NS
Maximum duration Suck sustained at a negative Pressure of -30mmHg (secs)	28.9	27.8	NS
Duration of intersuck interval (secs)	26.9	43.3	<0.05

Table 8.7 Suck pattern in infants with cord pH ≤ 7.0 according to those with *NE and those with no *NE

Parameter	NE*	No NE*	
	5 infants	12 infants	p value
Total frequency of strokes over 5 min epoch	64.3	76.2	NS
No. of strokes according to a negative pressure category			
0 to −10mmHg	46.5	18.5	<0.05
10 to −20mmHg	11.5	9.02	NS
-20 to −30mmHg	6.25	48.6	<0.01
Maximum duration Suck sustained at a negative Pressure of -30mmHg (secs)	0.06	57.7	<0.001
Duration of intersuck interval (secs)	40.1	14.5	<0.05

*NE denotes Neonatal Encephalopathy

Table 8.8   Suck pattern in infants without NE* according to those with cord pH≤ 7.0 and those with cord pH 7.01-7.25

Parameter	pH≤ 7.0	pH 7.01-7.25	
	12 infants	34 infants	p value
Total number of strokes over 5 min epoch	76.2	96.9	NS
No. of strokes according to a negative pressure category			
0 to –10mmHg	18.5	36.06	NS
-10 to –20mmHg	9.02	2.75	NS
-20 to –30mmHg	48.6	58.1	NS
Maximum duration Suck sustained at a negative Pressure of -30mmHg (secs)	57.7	136.65	<0.01
Duration of intersuck interval (secs)	14.5	30.4	NS

*NE denotes Neonatal Encephalopathy

Table 8.9   Heart Rate Variability (HRV) in infants with *NE according to those with cord pH ≤ 7.0 and those with cord pH 7.01-7.25

Cord pH	No. of infants with NE*	Mean HRV (SD) millisecs	p value
≤ 7.0	5	490 (61)	NS
7.01-7.25	11	498 (75)	NS

*NE denotes Neonatal Encephalopathy

Table 8.10   Heart Rate Variability (HRV) in infants with cord pH ≤ 7.0
according to those with *NE and those with no *NE

Clinical Status	No. of infants cord pH ≤ 7.0	Mean HRV (SD) millisecs	p value
With NE*	5	490 (61)	NS
No NE*	11	539 (43)	NS

*NE denotes Neonatal Encephalopathy

Table 8.11 Heart Rate Variability (HRV) in infants with no *NE according to those with cord pH ≤ 7.0 and those with cord pH 7.01-7.25

Cord pH	No. of infants no NE*	Mean HRV (SD) millisecs	p value
≤ 7.0	11	539 (41)	NS
7.01 – 7.25	32	550 (24)	NS

*NE denotes Neonatal Encephalopathy
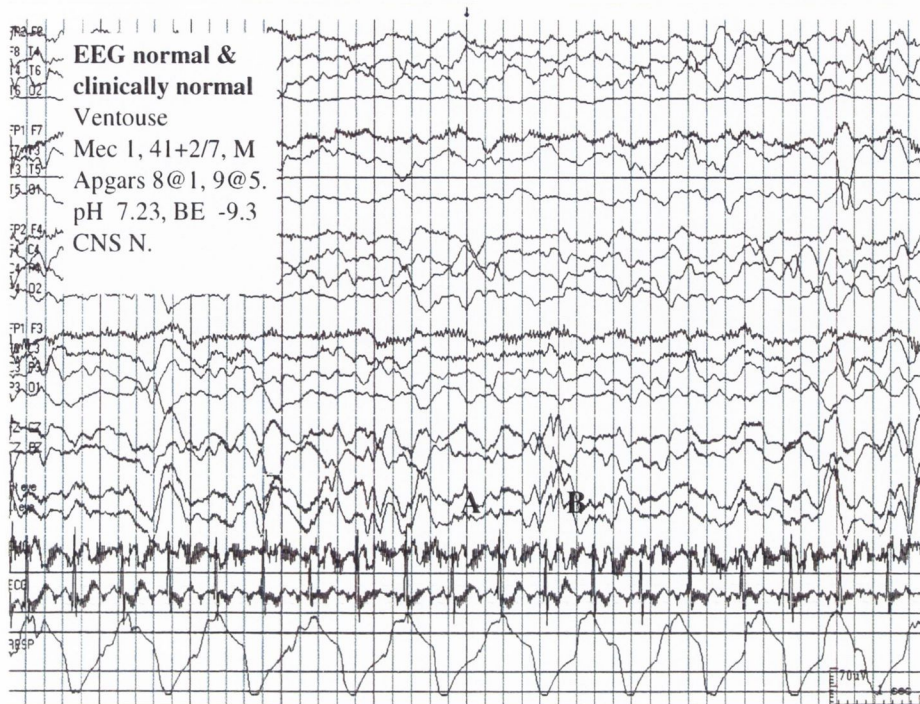
Fig 8.1   10 second epoch of quiet sleep portion of normal EEG. Note the trace alternant pattern: runs of high amplitude (A), followed by runs of low amplitude (B) which last 2-3 seconds maximum.
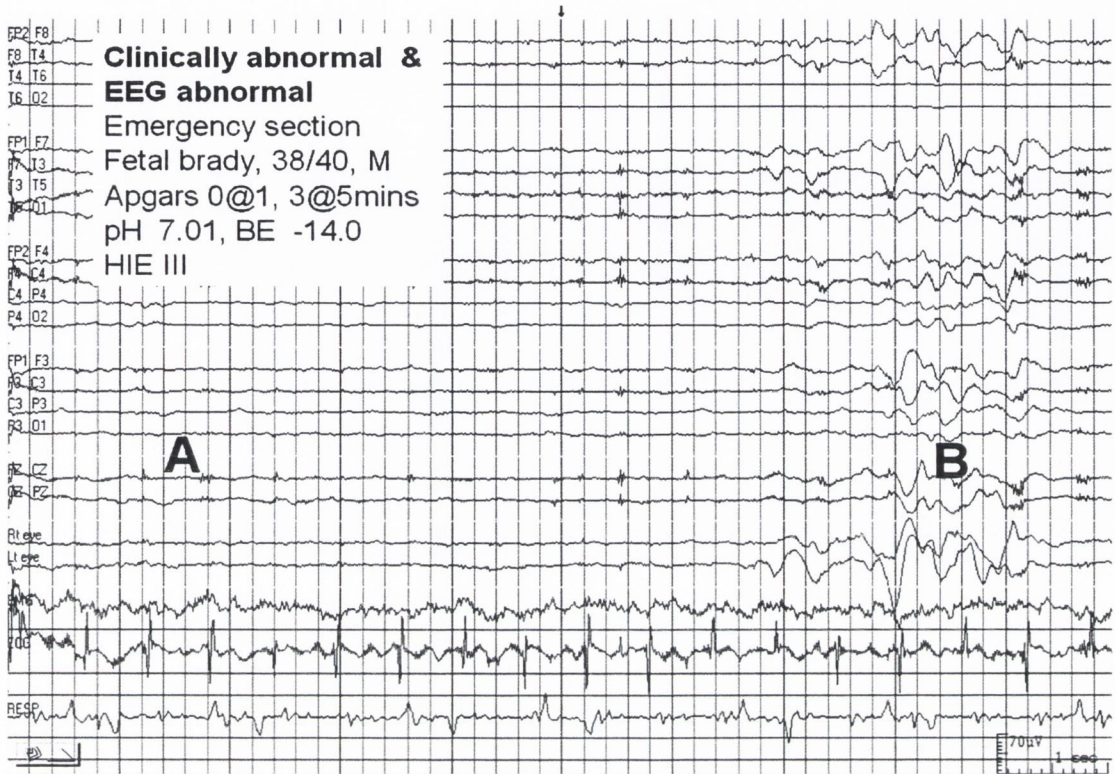
Fig 8.2   10-second epoch of quiet sleep of severely abnormal EEG. Note
the burst suppression pattern: Runs of low amplitude (A) lasting 20-
30seconds followed by bursts of higher amplitude (B).

The following text appears within the EEG chart:

**Clinically normal &
EEG abnormal**
Emergency section
39/40, M,
Apgars 2@1, 7@5mins
pH 6.9, BE -15.6

A

B

Fig 8.3   10-second epoch of quiet sleep of EEG of clinically normal infant who was acidotic at birth. Note the much longer low amplitude portions (A), lasting 6-10 seconds and the much higher amplitude of the bursts (B) compared to normal quiet sleep (Fig 8.1)

Fig. 8.4   Suck pattern of well infant. Emergency section for Foetal distress. Apgars 9@ 1 min., 9@ 5 mins., Cord pH = 7.15. Normal Clinical exam and normal EEG. Note how most of the sucking strokes reach the maximum pressure level (-30mmHg) and the length of time that the suck is held @ -30mmHg (75 seconds).
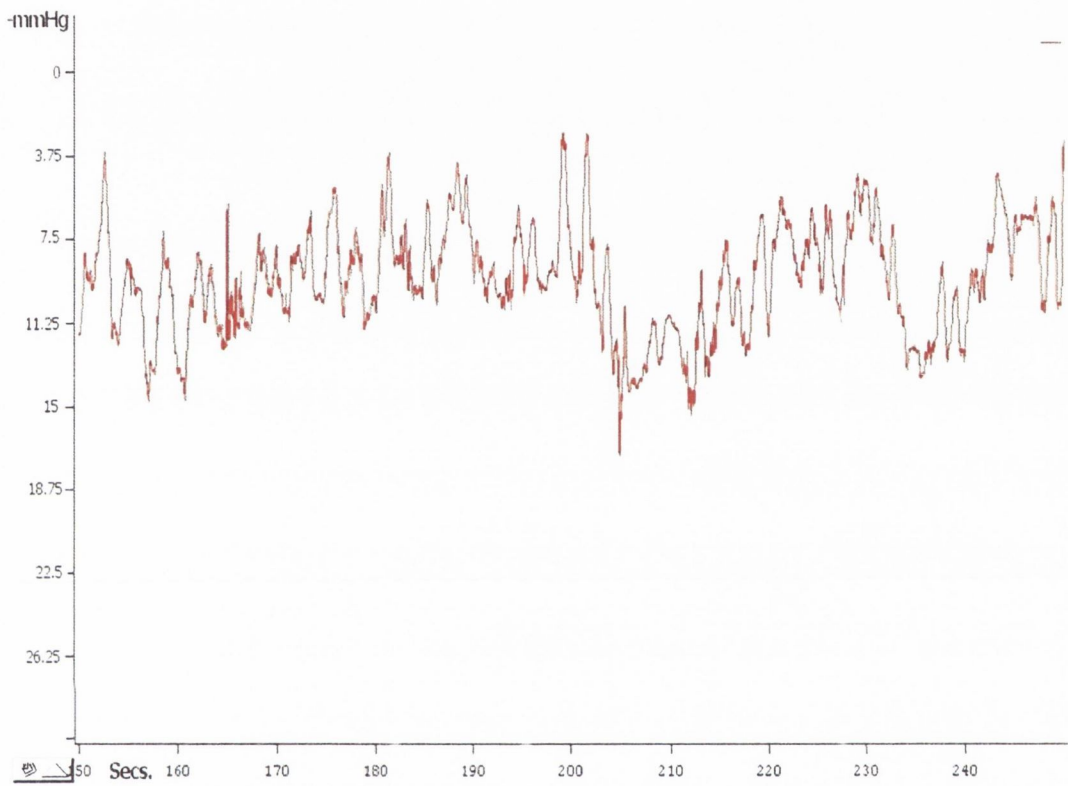
Fig. 8.5   Suck pattern of ill infant. Emergency section for Foetal distress and ruptured uterus. Apgars 0 @ 1 min., 3 @ 5 mins., Cord pH = 6.8. Clinically NE Sarnat III, cranial ultrasound and MRI –bilateral thalamic infarcts. EEG severely abnormal. Note how none of the strokes reach the maximum pressure of -30mmHg and how none of the strokes are held for more than a few milliseconds.

CHAPTER 9

DISCUSSION

9.1 Introduction: The Measurements Employed

9.1.1 EEG While the EEG has been known for some time to be a very useful tool in neonates with encephalopathy (Sarnat HB *et al,* 1976; Watanabe K *et al,* 1980; Holmes GL *et al,* 1983, 1993; Wertheim D *et al,* 1994; Murdoch-Eaton *et al,* 1993; Hellstrom-Westas L *et al,* 1995; Biagionoi E *et al,* 1998, 2001; al Naqeeb N *et al,* 1999; Toet MC *et al,* 1999.) it is not readily available in most neonatal intensive care units. In the majority of cases when an EEG is performed in the neonatal period it is too late, i.e. after the first 3-4 days when the infant is clinically stable for transfer. This is unfortunate because the EEG is a highly sensitive tool, which as illustrated quite clearly in my thesis was able to detect sub-clinical encephalopathy. It is also a very safe test being non-invasive and only disturbing the infant during application and removal of electrodes, all other activities such as administration of drugs, feeding and neonatal care may be carried out during the recording.

Interpretation has improved over time with concordance and correlation for analysis between observers being almost 100%. I had 95% correlation between my analysis of the EEGs in this study and that of the independent analyser (BL). There are normal reference ranges available for amplitude, frequency, number of sharp waves etc., according to gestational age. EEG patterns are different between pre-term and term infants. Burst suppression is considered normal in a 26 week premature infant, but always abnormal at term.

9.1.2 *Manometric Suck Integrity*   The suck reflex in newborns is complex. It can be difficult to ascertain the underlying problem when a baby feeds poorly. The suck reflex is under the control of the cranial nerves IX, X and XI. An inadequate suck in a term infant can signify a neurological problem. In particular abnormal suck integrity is encountered in infants with neonatal encephalopathy (Volpe JJ, 1995).

Many of the studies about the neonatal suck response were performed in the 1950's and 1960's (Gryboski D, 1969; Andran GM *et al,* 1958a, 1958b; Bosma JF, 1967; Kron RE *et al,* 1966; Schachter F, Apgar V, 1959; Colley JRT, Creamer B, 1958; Brechtl HFR *et al,* 1967). The full-term infant sucks at a rate of once per second and swallows approximately every five to six sucks (Ramsay M *et al,* 2002; Dubignon J, Cooper D, 1980). Swallowing begins as early as 11 weeks gestation and mouthing movements, the forerunner of sucking activities, may be elicited by 18 weeks. Sucking and swallowing develop rapidly after 34 weeks gestation (Wolff PH, 1968). There are rhythmic negative intraoral pressures that do not result in the delivery of milk classified as non-nutritive whereas those that provide milk are nutritive (Lucas A *et al,* 1981;Ramsay M, Gisel EG, 1996). Gryboski, defined three stages in development of sucking (Gryboski JD, 1969). The first is mouthing alone; the second is short bursts of four to seven sucks, and the third is characteristic of the full term infant who has prolonged bursts of at least 30 seconds. Through their use of cineradiography studies Andran and colleagues demonstrated that there is usually a rhythm of one breath to one or two swallows (Andran GM *et al,* 1958a, 1958b).

9.1.3 Heart Rate Variability   The clinical relevance of heart rate variability (HRV) has been appreciated since the mid 1960's (Hon EH, Lee ST, 1965). It is a complicated mathematical way of assessing autonomic function that has only really become clinically applicable since the advent of computer software packages that process the complex calculations. These packages also allow one to select segments of the recording that can be removed from the final calculation because of excess movement artefact. HRV has been mainly used in adult medicine for assessment of myocardial infarction damage and diabetic neuropathy (Kleiger RE *et al*, 1987; Ewing DJ *et al*, 1985), it's only documented use to date in infants is with Sudden Infant Death Syndrome and sepsis.

9.2   Technical and novel aspects

9.2.1 EEG

Conventional analogue instruments consist of an amplifier, a galvanometer and a writing device. A pen mounted on the galvanometer moves up and down each time the coil moves. The pen draws the trace onto paper moving below it. The sensitivity controls the size of the activity displayed. For example a sensitivity of 10 µV/mm means that a signal with amplitude of 100 µV will produce a 1 cm vertical deflection. A digital EEG system converts the waveform into a series of numerical values. This process is known as Analogue-to-Digital conversion. The values can be stored in the computer memory, manipulated and then redisplayed as waveforms on a computer screen. The rate at which the waveform data is sampled in order to convert it into a numerical format is known as the sampling rate. The sampling rate is usually expressed in Hz, for example 240 Hz is 240 times per second. The minimum acceptable sampling rate is 2.5 times greater than the highest frequency of interest but most digital EEG systems will sample at 240 Hz.

The main advantage of digital versus analogue recordings is not simply the improved quality and accuracy of the recording because of the increased sampling, but the ability to alter the montage after the recording. This improves the accuracy of the analysis and interpretation, especially if there is confusion between artefact and abnormal patterns. EEG signals that have been digitised can be manipulated to change the montage 'on-line' at the time of recording or 'off-line' after the recording is completed. This 'remontaging' is accomplished by recording all EEG channels with a common reference electrode. Regardless of the montage used to display the data while it is being recorded, data is stored into the computer memory in common reference mode. This allows the data to be displayed using different montages at a later time. Since digital systems store the analogue signal as numerical values, remontaging is a simple subtraction process, which results in cancellation of the common reference.

The majority of studies over the last 20 years have used amplitude integrated EEG technology (Murdoch-Eaton *et al*, 1993; Hellstrom-Westas L *et al*, 1995; Biagionoi E *et al*, 1998, 2001; al Naqeeb N *et al*, 1999; Toet MC *et al*, 1999). This uses 3 scalp electrodes and therefore gives a limited impression of the brainwave pattern. The digital EEG technology I used in this study used 19 scalp electrodes, 9 ancillary electrodes – 2 eye, 2 EMG (sub mental chin electrodes), 2 ECG, 2 frontoparietal, 1 respiratory, a ground and reference electrode. This use of ancillary and 19 scalp electrodes gives a more accurate and complete representation of the newborn's brainwave activity. It is the gold standard neonatal montage as the ancillary electrodes allow one to decipher the infant's sleep state. The extra scalp electrodes give one a parasagittal image (F3, C3, P3, O1, F4, C4, P4, O2) of the infant's brain. The overall effect is a more detailed recording, which as my thesis demonstrates is capable of detecting subtle abnormalities.

One of the major technical difficulties with analogue recordings was impedance. Outside common signals such as mains electricity (50Hz) was often very difficult to remove and as one had only one hard copy paper recording there was no means of altering this at a later date. With digital EEG machines the filters are much more successful at reducing impedance and indeed artefact, but also have the advantage of altering sensitivity after the recording if interference becomes apparent. In my thesis this was very useful when infants were on high-frequency ventilation. The Neonatal Intensive Care Unit had filters in place for mains frequencies. The EEG machine was able to filter most artefact and impedance including conventional ventilation interference. However, I experienced difficulty filtering out the high-frequency ventilation (10Hz) at the time of recording, but was able to filter it out during analysis.

The other novel aspect of this thesis was that I coined a numerical system of analysis. Conventional EEG analysis would report an EEG as normal, mildly, moderately or severely abnormal. While this system is useful in clinical practice, it is very limited when comparing data and statistically analyzing it. It also limits the detection rate for differences between study groups. I chose a 10 second epoch of each sleep state for each infant and then systematically measured the maximum and minimum amplitude for each channel, as well as the overall number of sharp waves per 10 second epoch. I also measured the percent time each infant spent in each of the three sleep states and whether synchrony occurred or not. As a prolonged interburst interval has been previously reported as a poor prognostic indicator of long-term outcome (Holmes GL *et al,* 1983, Grigg-Damberger MM *et al,* 1989), I also measured this low amplitude portion of quiet sleep for each infant. This system of analysis proved very useful in my thesis because there was a difference in the values between cases and controls

especially during Quiet Sleep. The numerical values allowed accurate statistical analysis and interpretation

9.2.2 *Manometric Suck Integrity*

The time taken to re-establish teat feeds is employed as a prognostic indicator and the manometric technique used in this thesis can be helpful in the confirmation of sucking dysfunction. It gives insight into the different suck patterns that are encountered in infants with and without neonatal encephalopathy. The analysis in my thesis provides information into the suck mechanism and how it is affected in the presence of encephalopathy.

The suck components that my technique demonstrated were suck frequency, maintenance of a significant negative pressure and the interval between bursts of sucking. In the face of encephalopathy all these parameters are affected.

9.2.3 *Heart Rate Variability (HRV)*

I examined heart rate variability patterns in neonates with and without encephalopathy. Technically the main difficulty was not in the calculation of the HRV, but in the quality of ECG recordings. As aforementioned the first 15 infants had sub-optimal recordings until I discovered that EEG electrodes gave better quality tracings than normal ECG leads.

9.3   Strengths of The Study

One of the strengths of the thesis was the population size. The National Maternity Hospital has a birth cohort of 8,500 births annually. The institution is a tertiary maternity hospital with a long history of interest in labour management. It practises an "Active Management of Labour" policy. The much unified labour ward protocols, which are under the

supervision of the Master means the practice of labour management was reproducible and consistent throughout the study.

Cord pH and scalp pH measurements have been part of the hospital's practice since the 1970's. The midwives are skilled at taking venous and arterial cord blood samples. This permitted verification that the sample for analysis was truly arterial.

The research was sited with all equipment in close proximity to the delivery suite, post-natal wards and neonatal intensive care unit (NICU).

An experienced Paediatric neurologist who was blinded as to the clinical status of the infant and their cord pH value carried out conventional EEG analysis.

There was a resourceful and innovative bioengineering department at my disposal. I was assisted in sourcing of a digital EEG machine, the design of the sucking apparatus and in the sourcing of the "dataplore" software to calculate heart rate variability (HRV) and suck pressure and frequency values. This ensured that the equipment used to calculate and record data was of a high standard and always accurately calibrated.

Before the study commenced I received formal practical training in EEG application and recording from the chief EEG technician at The Children's University Hospital, Temple Street. This ensured that I had developed appropriate skills in electrode placement, high standard of EEG recordings, the recognition of artefact and how to remove it from recordings and the ability to recognise the different sleep states and any overt abnormalities such as severe burst suppression or continuous seizures before even one infant was recruited into the study.

I was the only person recording the EEGs throughout the course of the study and this eliminated inter-observer variation.

I was fortunate to have the assistance of a distinguished and eminent statistician –Professor Leslie Daly- who from the outset meticulously helped me devise the study design before the research commenced. This ensured a good estimate of sample size calculation, ensured adequate number and randomisation of "control" or normal infants and ensured objective analysis of interim results to detect any possible errors or weaknesses in the study design.

My supervisor being a consultant Neonatologist allowed clinical access to patients and meant on site daily supervision of research.

Population
- Ideal source
- Setting for the research was favourable
- The annual number of births of 8,500 provided a large cohort that could be obtained within the time constraints
- The families were very supportive and there was no refusal to participate
- Specialist nature of the hospital meant that it was easy to track infants during their transit from labour ward to post-natal ward and/or neonatal intensive care.

EEG
- Digital EEG meant higher quality EEG recordings when compared to analogue.

- The complete 30-lead channel EEG recording meant a complete waveform from all areas of the brain. This improved the quality of the recordings and their ability to detect subtle abnormalities when compared to amplitude-integrated EEGs.

- The use of accessory leads i.e. eye leads, respiratory and EMG chin electrodes allowed accurate detection of the infants sleep state.

- The use of a video incorporated machine meant that any confusion between movement artefact and true seizure activity could be easily deciphered.

- Independent analysis by a consultant paediatric neurologist with a specialist interest in EEG ensured an unbiased, high quality and accurate interpretation of the recordings.

The National Maternity Hospital has a long research interest in labour and its active management. The textbook "Active Management of Labour", sets out a policy of management which is not only practised in the hospital but is replicated internationally in many units.

The hospital has long felt that a clear labour ward policy helps to reduce caesarean section where it is unnecessary. In addition to the concept of the "individual birth attendant" to each mother there is ready resource to scalp pH measurements whenever there are non-reassuring elements to the CTG.

Cord blood arterial and venous samples are universally obtained for every birth involving instrumental or operative delivery. The hospital piloted cord blood gas evaluation as early as the 1970s, thus all the perinatal staff is very used to obtaining cord blood gases and collating the results.

Indeed while I was a perinatal fellow doing my six months in obstetrics I was struck by how labour and its outcome were being evaluated with scalp and cord blood gas estimations. This subsequently led to my interest in this area. I set out in this thesis to establish the relationship between cord blood gas values and infants short-term outcome.

9.4   Problems and Challenges

The main problems I encountered during this study were of a practical and technical nature. Firstly, it was technically very challenging to apply such large numbers of electrodes when infants were vigorous and active. As no neonatal EEG is complete without a Quiet Sleep recording some recordings took longer than the standard one hour to ensure that the infant drifted into Quiet Sleep. It was not always possible to record Quiet Sleep especially with the healthy control population. Firstly they were more vigorous and active and therefore less likely to drift into quiet sleep and secondly, as they were not ill and residents of NICU I only had access to them for 2-3 hours maximum. I soon realized that the best time to perform EEGs in healthy infants is post feed, when they are much more likely to sleep. I also needed the help of a nurse when applying electrodes especially the posterior leads.

As mentioned previously high-frequency ventilation proved an unforeseen problem as it caused interference that was technically difficult to remove. The whole procedure was in itself time consuming. It took 20 minutes to set up the machine and apparatus, on average 30 minutes to apply the electrodes, a minimum of 60 minutes for recording the EEG and often 90 minutes to 2 hours in order to capture all sleep states and 20 minutes to remove the electrodes and clean them. Numerical EEG analysis took 30 minutes per infant and then a further 15 minutes per infant for independent observer analysis (BL).

The practical problems that I encountered were:

1) Ensuring that those healthy infants recruited from the post-natal ward were pre-feed, awake and alert prior to the recording,

2) Co-ordinating the recording with the EEG recording and application of leads, so that one did not take infants away from mothers twice.

As a solution to this problem I started the EEG recording about 60-90 minutes prior to when the next feed was due. This ensured that in most cases Quiet Sleep was captured in the recording. When the EEG recording was complete I carried out the suck recording as the removal of EEG electrodes invariably woke the infant.

Finding software to calculate neonatal HRV took some time. Finding expert advice and support to guide me technically was difficult as there is very limited experience with neonatal HRV. The standard ECG leads removed little artefact, I soon realized that EEG electrodes gave a more refined ECG tracing. The other difficulty was deciding on a standard sampling time. I chose 5 minutes as all the literature would suggest either 24-hour/5minute recordings. I also chose Quiet Sleep -as confirmed by EEG- as this gave the least movement artifact.

9.5   The findings of the study

9.5.1 EEG

Quiet Sleep revealed the significant findings. In Quiet Sleep the EEG generally consists of: Trace alternant pattern, regular respirations, no eye movements, no EMG activity from sub mental (chin) electrodes and increased likelihood of abnormalities, such as excess of sharp waves. The other typical abnormalities which emerge during Quiet Sleep are: Seizures, excessive sharp waves (especially if persistently focal), decreased amplitude of background EEG, poor state differentiation,

asynchronous EEG activity, burst suppression and excessive discontinuity of background.

In this thesis I showed that in the face of definite encephalopathy (Sarnat II/III) the low amplitude portion of the trace alternant pattern in Quiet Sleep was prolonged and there were an increased number of sharp waves. These parameters were more markedly increased if there was co-existent severe acidosis (arterial cord pH value < 7.0). This correlation with cord pH value has never been reported before. A pattern of sub-clinical encephalopathy appears to be emerging. Those babies who were clinically normal but had a cord pH value of < 7.0 showed a tendency towards prolongation of the low amplitude portion of Quiet Sleep and increased number of sharp waves in quiet sleep, both of which were statistically significant.

It is important to appreciate that pH is a logarithmic function of the H^+ ion concentration. Thus a fall in pH from 7.3 to 7.2 is not as significant as a pH fall from 7.1 to 7.0. In the latter case there are twice as many free hydrogen ions generated. It is obvious from the table (table 1, chapter 1), that once the pH is below 7.0 the hydrogen ion concentration is twice normal (100$nmol/L$ Vs 50$nmol/L$). However not all infants born with pH values of 7.0 and below are asphyxiated.

In biological terms there must be a spectrum between the completely abnormal and the completely normal. The point at which abnormality becomes manifest is a matter of contention. pH and acidosis offers an opportunity to assess this, as increasing acidosis and hydrogen ion concentration are indicators of hypoxemia. The value at which injury is more likely than not to happen is important in terms of prognosis and management.

Experimental literature that addresses the question of a critical threshold for oxygen saturation in the fetus is limited. Richardson and colleagues performed studies to elucidate this critical level[13]. From their data, it can be concluded that a critical threshold of oxygen saturation exists for fetal hypoxia. The critical threshold value of oxygen saturation above which the fetus does not demonstrate significant acidosis is approximately saturation 30%.

Richardson later expanded this study to include measurements of electro-cortical activity and breathing movements during prolonged and graded hypoxemia (Richardson B *et al*, 1992). The percent time spent in low voltage electro cortical activity averaged 53% +/- 1.4% with fetal $SaO_2 >$ 60% and showed a marginal decrease with SaO_2 between 30% and 60%. With $SaO_2 <30\%$ and a metabolic acidosis apparent in all but one animal, the fraction of time spent in low voltage electro cortical activity decreased to 35% +/- 4.1% on average.

A pH value of ≤ 7.0 appears to be a useful cut off point and has been described in the obstetric literature as "pathologic fetal acidemia". I have demonstrated in this thesis that when the pH is 7.01-7.25 and the infant is clinically normal, even in this high-risk group, the EEG is always normal. This study describes a novel finding previously unreported in the neonatal EEG. Infants with definite encephalopathy had higher amplitude and frequency of bursts during quiet sleep. These parameters were once again more markedly increased once there was co-existent severe acidosis (ie. cord pH ≤ 7.0).

My results highlight how sensitive a tool the EEG is in neonates not only for detecting abnormal patterns in clinically encephalopathic and neurologically impaired infants, but also for detecting subtle changes in the face of severe acidosis. This study prospectively confirms that a cord pH value of 7.01-7.25 appears safe once the infant is behaving normally, but that the small subset of infants who have pH values ≤7.0 and behave normally warrant closer investigation and long-term follow up. Studies in the last 20 years have mainly focused on amplitude integrated 3 lead EEGs. By using 30 lead digital technology the discriminatory and diagnostic potential of the EEG can be considerably enhanced. This will ultimately not only improve our knowledge and understanding of neonatal encephalopathy and highlight pH thresholds that warrant obstetric intervention and also expand our understanding of the window of vulnerability for the neonatal brain.

9.5.2 *Manometric Suck Integrity*

Normal babies have a suck frequency 115 strokes per 5 mins. Babies with neonatal encephalopathy do not suck as frequently and exhibit rates only two thirds that of normal infants. The suck effectiveness is also impaired. They are unable to generate a sufficiently negative pressure for optimal feeding. Achievement of negative pressures between minus 20mmHg to minus 30mmHg is the predominant pattern in normal babies. Infants with encephalopathy fail to reach these values. Another feature was the babies with neonatal encephalopathy were unable to maintain a negative pressure for more than a few milliseconds compared to 20 seconds in normal infants. The interval between bursts of sucking was much longer for babies with neonatal encephalopathy 38 seconds compared to 14.45 seconds in normal infants.

My findings demonstrated that the disruption of the suck reflex in term infants with encephalopathy is quite complex. They do not suck as frequently. They are unable to generate or maintain an effective negative pressure. The duration between sucking bouts is abnormally long.

9.5.3 Heart Rate Variability

There was no difference in the mean HRV between infants with and without neonatal encephalopathy. There was also no difference between infants based on cord pH values. Given that very significant differences showed up on subtle tests such as EEG and suck manometry it is instructive that no difference was manifest in HRV values. I feel that the results of this study bring into question the subtlety of HRV as compared to EEG and other tests of neurological function. My thesis shows no difference soon after birth even between severely encephalopathic and clinically normal neonates. When one considers that all other tests used in the study - clinical examination, EEG and suck manometry- were all able to identify differences between groups based on pH values, the role of HRV and indeed myocardial damage in the face of acidosis and/or encepahlopathy is dubious. It is also worthy of consideration that HRV is the obstetricians main tool for the detection of asphyxia during labour.

9.6 Implications

If the arterial cord pH value is 7.01-7.25 and the infant is behaving normally then the EEG is always normal. Therefore, even if infants from this group later go on to develop subtle neurodevelopmental problems such as learning difficulties; it is unlikely to be due to any perinatal insult in the face of normal early neonatal behaviour and a normal EEG recording.

However, in the small subset of infants who are severely acidotic (arterial cord pH value ≤ 7.0) EEG abnormalities are present even when the infant behaves normally. This subset of infants needs careful follow up because these subtle EEG changes could be markers of later problems. A pH ≤ 7.0 increases the likelihood of developing encephalopathy 16 fold. As a group infants with a cord pH value ≤ 7.0 who are encephalopathic have more marked EEG abnormalities. The challenge to obstetricians is to identify these infant-mother pairs prior to delivery and to deliver them before the pH drops below 7.0. From my analysis of patient data it is clear that primigravida women and induced deliveries have a statistically significant greater risk of developing a pH ≤ 7.0. Had these infant-mother pairs been identified and thus a severe acidosis avoided, then the number of infants in my study with a pH ≤ 7.0 would have been almost halved.

Infants with significant acidosis and a cord pH value ≤ 7.0 have demonstrated EEG abnormalities in the absence of any clinical manifestations. It is tempting to postulate that the proportion of babies with this degree of acidosis have a mild degree of encephalopathy. The EEG characteristics of this subgroup were readily identifiable and reproducible. The changes are manifest in the Quiet Sleep state and the most repeatable finding is the prolonged interburst interval i.e. low amplitude portion of quiet sleep.

In addition those babies with a pH ≤ 7.0 and clinical encephalopathy demonstrated a more exaggerated but similar EEG finding. I propose that

there is a spectrum from sub-clinical to clinical encephalopathy in this group of extremely acidotic infants.

On the other hand this thesis has demonstrated that infants with a pH in the 7.01-7.25 range who are non-encephalopathic have not shown these EEG changes. Which is reassuring as only a small number of infants even in high-risk deliveries reach a pH $\leq$ 7.0.

The design and time constraints of my thesis have meant that it has not been possible to undertake a formal neurodevelopmental follow up of these infants. This would clearly be of great interest and arrangements are being undertaken to do this.

This research has produced a new EEG finding i.e. higher amplitude and frequency of bursts in Quiet Sleep in infants who are encephalopathic; the finding is robust and repeatable.

Manometric recordings of the newborn infants suck provide useful additional information about the infant's sucking ability. Those with neonatal encephalopathy have major defects across a number of parameters.

This manometric sucking apparatus may be used in the future to monitor the sucking patterns of premature infants. It would aid the decision making of when to introduce teat feeds i.e. when the premature infant is approaching term values for pressure and frequency.

It may also be a useful tool in examining the grossly abnormal and frantic sucking pattern seen clinically, in infants of heroin abusing mothers.

Finally, in the face of encephalopathy one may be able to reassure parents that their infant will do well if the sucking parameters are within the normal range, once off all sedation. It may also aid speech therapists and nurses in the introduction of earlier oral stimulation to help encourage teat feeds, in those infants with severe encephalopathy.

As already suggested the main implication of the HRV findings in this thesis is that it is not a subtle tool. The use of HRV (in the form of CTG) in the antenatal diagnosis of fetal distress is routinely used. Given that there are no differences in HRV values between severely encephalopathic and clinically normal neonates and no difference in HRV between neonates based on cord pH values, yet there are significant differences between these groups clinically, in their EEG recordings and their sucking patterns, one has to question how this test could detect differences of any significance antenatally. Although I was not in a position to study CTGs, the lack of subtlety and interpretative power of HRV in the face of EEG abnormalities and cranial nerve dysfunction does suggest that HRV is a limited technique.

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