The Cerebrovascular Effects of Carbon Dioxide in Ventilator-Dependent Preterm Infants

by

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Dedication

This thesis is dedicated to Peter Butcher (1950 - 1979) and

Professor Tim McElwain (1937 - 1990).

"Morituri te salutamus!"

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Statement

The following thesis represents the original work of the author. The respiratory measurements in chapter 5 were carried out with the assistance of Dr David Field and the thermodilution assessments of cardiac output (chapter 7) were performed by Dr Ranjit Leanage. None of the work in this thesis has been submitted for a degree of another University.

Ethics

Ethical permission for the studies was given by the Leicestershire District Ethical Committee. Informed consent was given by the parents of all of the infants prior to the studies.

Abstract

Changes in arterial carbon dioxide tension ($PaCO_2$) have a major influence on cerebral blood flow (CBF). The following work firstly reviews the role of $PaCO_2$ and other factors which regulate CBF. Secondly a study was undertaken to assess whether changes in CBF following a 1 kPa rise in $PaCO_2$ predicted subsequent periventricular leukomalacia (PVL - identified on cranial ultrasound) in sick preterm infants, since PVL is an important cause of neurological deficit in such infants and has been hypothesised to occur from inadequate regulation of CBF.

Changes in CBF (estimated by Doppler cerebral blood flow velocity, [CBFV]) following a rise in $PaCO_2$ in the first day of life in infants ≤30 weeks gestation appeared greatly dependent on the concomitant changes in mean arterial blood pressure (MABP). Similar dependence also occurred following administration of pancuronium to infants whose CBFV response was previously independent of changes in MABP. This dependency lasted for the duration of paralysis. Changes in CBFV following a rise in $PaCO_2$ did not however predict subsequent ultrasonographic changes indicative of PVL.

Since serial studies on individuals were often performed at different ventilator settings, the circulatory effects of ventilatory rate in 20 therapeutically paralysed preterm infants were studied to determine whether fast rates might compromise MABP and hence CBF. At the fastest rates used ($100.min^{-1}$), changes in CBFV appeared influenced by changes in MABP. This again may have resulted from the use of pancuronium.

A Doppler technique was also used to study changes in cardiac output following a similar carbon dioxide (CO_2) "challenge" in 21 of the infants. The rise in MABP observed was not accompanied by a rise in cardiac output, suggesting that components of peripheral resistance influenced blood pressure in such infants.

These results firstly confirm the major cardio- and cerebrovascular influence of $PaCO_2$ in sick preterm infants. Secondly they underline the importance of continuous monitoring of and the avoidance of large changes in blood pressure in such infants. The circulatory effects of pancuronium warrant further study.

Contents

Abbreviations

ABP	Arterial blood pressure	IVH	Intraventricular haemorrhage
ACA	Anterior cerebral artery	MABP	Mean arterial blood pressure
aHb	Arterial haemoglobin concentration	MAP	Mean airway pressure
CBF	Cerebral blood flow	MCA	Middle cerebral artery
CBFV	Cerebral blood flow velocity	N_2O	Nitrous oxide
CO_2	Carbon dioxide	$PaCO_2$	Arterial carbon dioxide tension
CP	Cerebral palsy	PaO_2	Arterial oxygen tension
CPP	Cerebral perfusion pressure	PEEP	Positive end-expiratory pressure
CSA	Cross sectional area	PET	Positron emission tomography
CSF	Cerebrospinal fluid	PIP	Peak inspiratory pressure
CT	Computed tomography	PRF	Pulse repetition frequency
CVP	Central venous pressure	PVH	Periventricular haemorrhage
CW	Continuous wave	PVL	Periventricular leukomalacia
HB	Deoxygenated haemoglobin	PW	Pulsed wave
HbO_2	Oxygenated haemoglobin	RAP	Resistance area product
HFPPV	High frequency positive pressure ventilation	SaO_2	Arterial blood oxygen saturation
		SD	Standard deviation
IRDS	Idiopathic respiratory distress syndrome	SEM	Standard error of mean

Chapter 1

Introduction

Improvements in neonatal intensive care have resulted in the survival of many extremely preterm infants previously considered to have a very poor prognosis. This success in improving survival of ever smaller infants however has created problems of its own, for example neurological deficit. Cerebral palsy (CP) is the most prevalent severe disability in very low birth weight survivors and is often a cause of long term emotional and financial stress within a family in addition to requiring considerable input from both hospital and community services.

Certain specific forms of brain injury in preterm infants appear to be closely associated with subsequent CP. In particular, studies have shown a correlation between periventricular cavities and CP. One such study by Graham et al (1987) showed that the development of cysts in the periventricular white matter (identified prospectively using real time ultrasound scanning) predicted CP with an accuracy of 94%, the incidence of CP being 7.7%. Histologically (Trounce et al 1986b), these lesions represented cystic degeneration in areas of periventricular leukomalacia (PVL).

The evolution of studies linking PVL to neurodevelopmental deficit and the role of cranial ultrasound in detecting preterm cerebral injury are discussed in detail in chapter 2. However in brief, PVL is thought to result from infarction of the periventricular white matter, which is a relative vascular watershed. It has been hypothesized that PVL develops if cerebral blood flow (CBF) is not regulated in the face of a fall in blood pressure, but the exact pathophysiology of its development remains incompletely understood. In addition, little is known about the degree to which preterm infants are

capable of regulating CBF, or whether the extreme preterm infants who now constitute an increasing proportion of the workload of neonatal intensive care units respond differently compared to their more mature counterparts.

Clearly then an understanding of the anatomy and physiology of the cerebral circulation in the preterm newborn and the changes that occur with maturity are essential to any consideration of perinatal cerebrovascular pathology. CBF depends firstly on the cerebral perfusion pressure (CPP), which in turn depends on systemic arterial pressure, intracranial pressure and central venous pressure (CVP). In addition however, there is a degree of intrinsic control of blood flow within the cerebral circulation mediated by changes in cerebral arteriolar diameter, which in turn affects cerebrovascular resistance. This is discussed further in chapter 3.

One important factor mediating cerebral arteriolar diameter and hence blood flow is arterial carbon dioxide tension ($PaCO_2$). Adult studies have demonstrated that a rise in $PaCO_2$ results in a rise in CBF (Kety & Schmidt 1948). Levene et al (1988) studied the effects of a 1 kPa rise In $PaCO_2$ in 19 preterm infants who were being ventilated for idiopathic respiratory distress syndrome (iRDS). Using cerebrai blood flow velocity (CBFV) as an index of CBF, they demonstrated that even extreme preterm infants respond in a similar manner to adults. However, 6 out of the 19 infants studied showed a fall in CBFV in following the rise in $PaCO_2$. This apparent faii in blood flow was thought to be an abnormal response, and of these 6 infants, 3 subsequently developed PVL, whereas all of the remaining infants, who showed either no change or a rise in CBFV, had normal cranial ultrasound appearances. The induced rise in $PaCO_2$ was deemed unlikely to have caused the PVL, since firstly the $PaCO_2$ was not changed outside of the normal range and secondly a change of 1 kPa is probably representative of normal daily fluctuations in infants being

ventilated for IRDS. These observations warranted further study and the main question to be addressed by the following work was whether the degree or nature of the cerebrovascular response to a rise in $PaCO_2$ in a large group of ventilated preterm infants would predict subsequent development of PVL (chapter 7). There were several other issues to be considered prior to this, which were as follows:

(1) Which method of assessment of CBF would be most suitable for the questions being asked (chapter 4)?

(2) How might potential effects on CBF of repeated infant handling during studies be minimised (chapter 5)?

(3) Were there cerebrovascular effects resulting from changes in ventilatory parameters (chapter 6)?

The results of these studies suggested a key role for blood pressure in determining changes in CBF in sick preterm infants. It therefore seemed essential to examine factors affecting blood pressure, namely peripheral resistance and cardiac output. Peripheral resistance has several components (cutaneous and visceral circulations) and is thus difficult to measure in its entirety. Cardiac output however is dependent only on heart rate and stroke volume. The former parameter is easily measured and stroke volume may be estimated by considering it as the distance the ventricular stroke moves a column of blood ("stroke distance"). This may be estimated using Doppler ultrasound. A study examining the reproducibility of such a method of assessing cardiac output and its subsequent application in the neonatal setting to examine the cardiovascular effects of changes in $PaCO_2$ is presented in chapter 8.

Chapter 2

Brain Injury in the Preterm Infant

2.1 Introduction.

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2.1 Introduction

In this chapter the problems of (a) defining the overall prevalence of CP and (b) identifying aetiological factors are discussed. This is followed by a review of historical

studies recognising the association between preterm birth, brain injury (both IVH and parenchymal changes) and subsequent handicap. Secondly, the histopathological appearances of PVL and periventricular haemorrhagic infarction are described. In addition the use of computed tomography (CT) and ultrasound scanning for studying the evolution of pathological changes within the brain in vivo and their accuracy in the prediction of subsequent handicap is discussed.

2.2 PVL and CP

(a) Epidemiology

There are several difficulties which arise in assessing the distribution and size of the problem of CP. Firstly, it is not a specific condition with a single aetiology (although there may be considerable overlap between different forms [Hagberg & Hagberg 1984 & see below]) and has a wide spectrum of severity. Secondly, the disabilities resulting from CP become apparent with age, resulting in problems with ascertainment. Affected infants may die before a diagnosis is made, or may be so minimally affected that the condition is not recognised. For example, the prevalence of CP in East Scotland rose from 1.54 to 2.04 per 1000 between the age ranges of 0-4 and 5-14 years, as more cases became apparent with the demands imposed by school work (Henderson 1961). Studies by Harris (1987) and Piper et al (1988) on infants felt to be at high risk of developing CP highlighted the problems of attempting to make an early diagnosis of CP.

Even if age-specific prevalence is used, the method of data collection can greatly influence results. In New York, prevalence in the 5-14 year age group varied from 3.6 to 5.8 per 1000 depending on whether data were obtained from use of facilities or from door-to-door enquiry (Levin et al 1949). Nelson and Ellenberg (1982) also identified infants with "transient" CP who improved with age. Finally, differences in definitions and exclusion criteria make international comparisons difficult.

2.2(b) Aetiology

The association between prematurity and brain injury has been recognised for many years. Joerg (1826) noted that " too early and unripe born fetuses may present a state of weakness and stiffness in the muscles persisting until puberty or later ", and Little (1843, 1862) called attention to the fact that certain complications of the birth process resulted in mental retardation and bilateral spasticity. He described in particular "the influence of abnormal parturition, difficult labour, premature birth and asphyxia neonatorum" on such adverse outcome.

Little's work in particular established the view that CP resulted from adverse peripartum events and this has greatly influenced subsequent workers in both obstetric and neonatal fields. An alternative approach was taken by Freud (1897) who suggested that "Since the abnormal process of birth frequently produces no effect, one cannot exclude the possibility that, despite Little's anamnesis, diplegia might be of congenital origin. Difficult birth in itself in certain cases is merely a symptom of deeper effects that influence the development of the fetus". This view has gained more support in recent years in the light of findings from geographically defined populations as opposed to studies involving relatively few high-risk infants. Studies using these two approaches to the study of aetiological factors in CP will now be reviewed.

2.2b(i) Geographically Based Studies

Identification of all children with CP has been achieved in Western Australia since 1956. Stanley (1979) found that the incidence of CP varied with neonatal mortality, but did not find a marked improvement associated with changes in perinatal care, unlike contemporary studies from Sweden (Hagberg et al 1975). Over the study period (1956-75) however, there had been a change in the birth weight distribution within the popuiation, which may have influenced the reduction in CP. Other factors such as changes

in the population distribution of maternal demographic and biological characteristics (for example falling extremes of age and parity) and decreases in other risk factors may also have contributed to the changes in outcome. Further studies could not identify differences between the perinatal profiles of infants who ultimately developed CP and those who did not (Stanley & English 1986), supporting the role of antenatal factors. Although many infants with CP may have a history of intrapartum "asphyxia", Blair and Stanley (1988) felt that this was likely to be the cause in only 8% of 183 children with CP born between 1975 and 1980. This again supports the idea that CP may be multifactorial in origin. Most recently, Stanley and Watson (1992) reported the trends in perinatal mortality and CP between 1967 and 1985. Despite falls in both stillbirth and early neonatal mortality rates, the total CP rates remained relatively constant at around 2-2.5/1000 live births. Thus major obstetric interventions aimed at reducing birth asphyxia had not resulted in lower rates of CP, suggesting that asphyxia is not a major cause. However, CP rates rose in infants <1500g birth weight, which the authors felt might be attributable either to prenatal damage to the fetal brain or to postnatal complications of immaturity.

Powell et al (1988a &1988b) examined perinatal factors in 1048 infants with a birth weight <2000g who were found to have hemiplegia (n=16) or spastic diplegia (n=20) when seen at the age of 3 years or more. Whilst hemiplegia was strongly predicted by ante- and intra-partum factors, the association between diplegia and maternal factors was much weaker and the best predictor was low gestational age. Two major problems with these studies acknowledged by the authors was that routine ultrasound scanning was not being done throughout the study period (1979-81; see 2.4 & 2.7) and that many factors may have had their association with CP diluted as a result of infants dying.

Although some studies have indicated that the overall prevalence of CP has not

greatly altered, within the low birth weight population there has been an increase in all types (Hagberg & Hagberg 1984, Pharoah et al 1987a). It is currently uncertain whether this increase in low birth weight infants has resulted from a simple increase in incidence, from improved survival or because of diagnostic bias because of follow up studies. Pharoah et al (1990) argued that if the reason is an increase in "duration" rather than incidence of the condition, improved survival resulting from intensive care has an important role. Once again this would enable the effects of antenatal factors to become manifest: intrauterine growth retardation for example has been implicated in the aetiology of CP by several studies (Alberman 1963, McDonald 1964, Atkinson & Stanley 1983, Nelson & Ellenberg 1986, Pharoah et al 1987b, Blair & Stanley 1990).

The issue is further complicated by the fact that many studies have grouped all forms of CP together, although their aetiologies may differ. A bimodal distribution of spastic diplegia with regard to birth weight has been identified by several groups (Childs & Evans 1954, Fuldner 1957, Dale & Stanley 1980, Pharoah et al 1987b). The authors of the last of these studies felt that this distribution may result from different pathological processes operating in preterm compared to term infants. There were a large number of growth retarded infants in the group as a whole and mothers of infants in their preterm group had a higher incidence of spontaneous abortion, stillbirth and low birth weight. Gestational age also shows a bimodal distribution and, although highly correlated with birth weight, it does have an independent effect.

Cooke (1990) found that preterm infants who subsequently developed diplegia differed in regard to antenatal factors from controls (cranial ultrasound tending to be normal), whereas infants who developed hemi- or quadriplegia needed the inclusion of postnatal variables including (frequently abnormal) ultrasound scans to differentiate them from controls. He suggested therefore that the site and nature of the causative

pathological lesions in diplegia and hemi-/quadriplegia might differ.

2.2b(ii) Neonatal Risk Factors

An alternative approach is to study the relevance of neonatal risk factors to CP in a group of "at risk" subjects. As mentioned in chapter 1, parenchymal changes (in particular cystic PVL) in low birth weight infants sustained during the course of neonatal intensive care were found to accurately predict subsequent CP. The recognition of pathological changes in the brain parenchyma at post mortem, their identification in vivo using ultrasound scanning and their significance on follow up will now be reviewed.

2.3 Periventricular Leukomalacia

(a) Historical Background

Pathological changes in the periventricular white matter were first described by Virchow (1867), who suggested that the diffuse fatty change and gliosis seen may have been due in part to infection, as the changes closely resembled those which occurred in babies born to mothers with smallpox or syphilis. This was despite the fact that none of these infants had cutaneous eruptions. In a series of papers over the following ten years, Parrot described periventricular infarcts, which he initially postulated as being the result of a "nutritional deficiency" (Parrot 1868), though another cause he considered later was vascular insufficiency (Parrot 1873). In addition he distinguished these "pale infarcts" from the fatty changes described by Virchow. Parrot's description of these changes differed very little from those of later investigators. Rydberg (1932) suggested that such white matter changes were related in some way to circulatory insufficiency at delivery and noted that (especially in preterm fetuses) they did not appear to be haemorrhagic in nature. Schwartz (1961) postulated that venous stasis secondary to events during parturition played a role in pathogenesis.

Banker and Larroche (1962) reported a series of 51 infants with an approximately equal sex distribution who represented 19% of all infants dying at less than one month of age. All of these had periventricular white matter changes characterised by coagulation necrosis or infarction of the periventricular white matter and often had a history of apnoea or cardiac arrest. They proposed that this periventricular leukomalacia (PVL) was the result of hypoperfusion. Similar lesions could be produced in cats by experimental obliteration of the basilar artery and subsequent compression or closure of one or both carotid arteries (Abramowicz 1964). DeReuck et al (1972) suggested that PVL was a distinct clinical entity secondary to infarction in the "periventricular arterial end zones" between ventriculopetal and ventriculofugal branches of deep penetrating arteries. They described these lesions as being located 3-10 mm from the ventricular wall. The degree of development of these ventriculofugal arteries may be used as an index of cerebrovascular maturity (Takashima & Tanaka 1978).

2.3(b) Histopathological Appearance of PVL

Histologicaiiy, PVL is seen as circumscribed pale areas in the subependymal tissue adjacent to the lateral ventricles, separated from the ventricles by a thin (1-2 mm) layer of intact gliai tissue. Preferential sites for PVL are the frontal regions, anterior to the frontal poles of the lateral ventricles and the parietal areas at the level of the foramen of Monro in the centrum semiovale. Involvement of the occipital radiations at the trigone of the lateral ventricles is always associated with extensive frontal and parietal lesions. The lesions are often multiple and bilateral, supporting the hypothesis that ischaemic lesions occur in the watershed areas of central and cortical vascular supplies in the boundary zones between the main cerebral arteries (DeReuck et al 1972, Pape & Wigglesworth 1979, Levene et al 1985, and see 2.4[a]).

At the microscopic level, the earliest changes seen are coagulation necrosis with

nuclear pyknosis and sponginess of the tissue, delineated by bright red staining with Periodic acid-Schiff (Banker & Larroche 1962). Some reports have noted haemorrhage (which may be massive) into the necrotic areas (Armstrong & Norman 1974). Subsequently, astrocytic and microglia proliferation occurs with accumulation of macrophages in the infarcted areas. Following reactive gliosis the lesions become well delineated and cavitation occurs with formation of cysts.

The term PVL was originally used to describe a distinct histological appearance of the periventricular white matter. Other histopathological studies have identified more subtle, diffuse white matter changes which may be termed PVL (Leech & Aivord 1974). They speculated that these lesions resulted from a gradient of vascular insufficiency right across the white matter (rather than the more localised regions described above) with hypoxia and metabolic acidosis as major contributing factors. Owing to their more diffuse nature, these may be less easy to identify histologicaliy. Gilles and Murphy (1969) also identified a more diffuse type of white matter injury, characterised by the presence of hypertrophic astrocytes and acutely damaged gliai ceils. Whilst a single aetioiogical agent for all cases could not be identified, the authors postulated whether hypoxia or nutritional deficiency might be contributing to this type of injury.

Paneth et ai (1990) studied the white matter necrosis in 15 preterm infants (mean birth weight 948g) dying after the first week of life. The changes were predominantly ischaemic in 11 infants, the remaining 4 being haemorrhagic. No large cavitating lesions were found and the necrosis was described as diffuse in 10 of the cases. Only 3 infants had lesions conforming to Banker and Larroche's description of PVL (see above) and the authors speculated whether this was in part due to differences between the study populations (only 40% of infants in the earlier study had a birth weight <2500g).

2.4 Neonatal Brain Imaging

(a) Background

From a histopathological standpoint therefore, the neonatal brain appeared to show particular changes following adverse clinical events. Clearly the next step was to identify such changes in vivo, follow their evolution and determine their clinical significance in surviving infants.

CT scanning has previously been used to identify lesions in the neonatal brain. IVH was easily identified and was found to occur more frequently than previously thought in surviving infants though the majority were clinicaiiy silent (Papile et al 1978). This method is limited by the non-portability of the scanner and the ionising radiation required. Additionally, there are potential problems in interpreting certain appearances seen in the neonatal period, which render its use in the diagnosis of PVL limited. Estrada et al (1980) reported areas of "low attenuation" in frontal or occipitofrontal areas on early CT scan in a group of 63 infants (of whom 33 were premature). Only 26 of the group were followed up and of these, 2 were neurologicaiiy abnormal. There were clinical indications to repeat the scans in 7 infants, including one of the two found to be neurologically abnormal; this was the only scan found to be abnormal, suggesting that the initial low attenuation areas may have been due to incomplete myeiination. Indeed, Flodmark et ai (1980a) found poor correlation between hypodense areas on CT scan and ischaemic damage diagnosed at post-mortem and suggested (1980b) that low attenuation was a normal finding in preterm infants. Other smaller series (Di Chiro et ai 1978, Hirabayashi et ai 1980) report similar poor correlation between CT findings and clinical outcome, though the populations studied were heterogeneous.

Ultrasound scanning revolutionised neonatal brain imaging, enabling repeated examinations to be made without the problems of ionising radiation. French et ai (1950,

1951) attempted to delineate cerebral structures using 'A'-mode ultrasound techniques and Lithander (1961) reported the use of a similar method to study healthy term infants. These early investigations did not produce real-time images and were more concerned with detecting midline shift or asymmetry in the brain substance, such as caused by tumours.

The advent of real-time imaging (where successive images are placed on a TV monitor and rapidly erased, producing an image in "real time") enabled progressive ventricular dilatation to be monitored (Skolnick et al 1979) and also allowed non-invasive diagnosis of IVH (Pape et al 1979). Initial reports used an axial approach through the temporo-parietal region, but soon afterwards the value of the anterior fontanelle as an accoustic window was recognised (Cooke 1979, Lipscombe et al 1979). The evolution of cerebral injury in vivo could thus be studied, but the new technique also caused considerable controversy as to the significance of the appearances seen, since although IVH was readliy diagnosed, parenchymal changes were more difficult to interpret (see 2.4[b] & 2.5).

Early reports concentrated on the extent ("grade") of IVH and degree of ventricular dilatation seen on ultrasound scan, but it later became clear that the periventricular white matter changes previously reported from post-mortem series were of equal if not greater significance. A case report of post mortem correlation of haemorrhagic PVL diagnosed by ultrasound before death was described by Hill et al (1982). Levene et al (1983a) reported the poor neurodevelopmental outcome in the survivors of 13 infants with cystic PVL diagnosed on ultrasound and subsequently (1983b) reported an incidence of cystic PVL of 4% in a group of 120 infants with birthweights <1500g. Other studies have reported slightly different incidences for this conditlon (5% - Bozynski et al 1985; 8% - Weindling et al 1985a; 2.3% - Calvert et al 1986) which may be the result in part of the gestational age groups studied. Different

definitions of lesions seen on scan further compound the difficulty of comparing one study with another (see 2.5 and 2.6). Cystic change was sometimes not seen until 10 weeks postnatally (Bozynski et al 1985) and a large proportion of those lesions developing after the second week of life appeared to follow on from acute events such as sepsis and necrotising enterocolitis (De Vries et al 1986).

2.4(b) Ultrasound Appearance of PVL

The earliest stage of PVL is seen on ultrasound examination as increased echodensity in the periventricular white matter, which should be seen in both coronal and parasagittal planes. Extrapolation of the appearances seen in intraventricular haemorrhage led early investigators to the conclusion that these areas were primarily haemorrhagic in origin, leading to the term periventricular haemorrhage (PVH). in addition, several studies have described PVH and PVL in the same brain (Armstrong & Norman 1974, Shuman & Seiednik 1980, Levene et al 1983b). Ultrasound and autopsy correlation studies have subsequently shown that these areas are infarctive in nature and haemorrhage at the site of infarction is not a prerequisite for ultrasound diagnosis (Nwaesei et al 1984). Whether all such lesions are primarily ischaemic as proposed by Rushton et al (1985) remains open to speculation. They may represent areas of diffuse change such as those identified by Leech & Aivord (1974; see 2.3[b]).

These periventricular echodensities may either resolve, or persist and subsequently undergo cystic degeneration, the latter generally occurring 2-3 weeks after the appearance of the echodensities. Cystic lesions may disappear after several months, leaving enlarged ventricles with decreased cerebral myelin (see 2.6[b]).

Persisting periventricular echodensity when seen in two planes was termed "flare" in a prospective study of 200 very low birthweight infants (Trounce et al 1986a).

This appearance had previously been described using a variety of terms, for example "echogenic periventricular halo" (Grant et al 1983) and "peritrigonal echogenic blush" (DiPietro et al 1986). Prolonged flare (>2 weeks' duration) was seen in 12% of Trounce et al's cohort and was found to be areas of gliosis and microcalcification at autopsy (Trounce et al 1986b). It is of interest that a macroscopically normal brain can show these profound microscopic changes, which appear echodense on ultrasound. The long term significance of these more diffuse changes in surviving infants has recently been reported (see 2.9).

Progression of "flare" (seen on ultrasound) to cystic PVL (confirmed at autopsy) was not found in a more recent study by Hope et al (1988). They speculated that this may have been due to differences either in management or between their population and that studied by Trounce et al. The authors also reported that small areas of PVL (diffuse astrocytic gliosis with or without myelin loss and/or focal necrosis) found at autopsy were not always seen on ultrasound. Similarly, Paneth et al (1990) identified parenchymal echodensities on serial ultrasound scanning during the first week of life in only 6 out of 15 infants subsequently showing white matter necrosis at post mortem (see 2.3[b]). Whether or not there are any clinical correlates of these "missed" lesions remains unknown.

2.5 Periventricular Haemorrhagic Infarction

This refers to haemorrhagic necrosis of the periventricular white matter, and in contrast to PVL has only been recognised more recently as a distinct entity. It often coexists with IVH and this led to the description of such lesions as being "extensions" of IVH. Several neuropathological studies have shown clearly that simple extension of IVH does not occur (Volpe et al 1983, Rushton et al 1985, Guzetta et al 1986, Armstrong et al 1987, Gould et al 1987) and that the lesion is a haemorrhagic infarction.

Gould et al (1987) described 9 out of 39 infants with IVH who had associated intraparenchymai haemorrhage. In 4 of these infants the intraparenchymai haemorrhage was severe and contiguous with the IVH, resulting in a degree of cerebral disruption that made ascertainment of pathogenesis impossible. However, in 4 of the remaining infants ependymal continuity was present and the intraparenchymal component consisted of multiple perivascular haemorrhages radiating into the white matter following the distribution of the medullary veins. In addition, marked ischaemia and coagulation necrosis were not present. Takashima et al (1986) also found that the haemorrhagic component tended to be most concentrated near the ventricular angle where the medullary veins become confluent and ultimately join the terminal vein in the subependymal region. Therefore periventricular haemorrhagic necrosis appears to be a venous infarction. Other mechanisms that have been suggested as contributory factors to the periventricular necrosis include:

(1) Local release of lactic acid (Pranzatelli & Stumpf 1985).

(2) Release of potassium from haemolysis (Edvinsson et al 1986; see 2.7).

(3) Impairment of periventricular blood flow secondary to increased intraventricuiar pressure (Batton & Nardis 1987).

Whilst periventricular haemorrhagic infarction is neuropathoiogically different from secondary haemorrhage into areas of PVL, distinguishing between the two lesions in vivo may be difficult and clearly the two lesions may coexist in the same individual. On ultrasound in the coronal plane venous infarction appears as globular or triangular echodensities radiating from the external angle of the lateral ventricle, and if bilateral is asymmetrical. As with PVL, cystic degeneration follows, but the tendency is to form single large cysts which do not disappear with time.

2.6 Neurodevelopmental Sequelae

(a) Intraventricular Haemorrhage (IVH)

Whilst it rapidly became apparent that IVH was a common finding in preterm infants, follow up studies have shown that IVH is not invariably associated with an abnormal outcome. Prior to the use of ultrasound scanning, follow up reports were biased towards infants with more obvious clinical presentations. Studies such as that by Krishnamoorthy et al (1979) showed outcome varied with the extent of the IVH (diagnosed on CT scan) but not with hydrocephalus per se. Isolated IVH without ventricular dilatation or parenchymal involvement was associated with a normal developmental outcome (Shankaran et al 1982, Papile et al 1983, Dubowitz et al 1984). Shankaran et al (1982) also found that parenchymal involvement was associated with a higher incidence of handicap than with ventricular dilatation. These authors felt that the degree of haemorrhage was the most important factor influencing outcome, which is supported by the findings of Catto-Smith et al (1985). The overall incidence of major disability in the latter study is however much higher than in most studies.

Stewart et al (1983) also found that the presence of cerebral atrophy was associated with a worse outcome and suggested that cerebral ischaemia might be an important factor in determining handicap, although ischaemic lesions were not identified on scans. Similar findings were reported by Papile et al (1983). it is important to note that these early follow up reports of poorer outcome associated with ventricular dilatation may have been as a result of the dilatation being due to incorporation of cystic parenchymal lesions into the ventricles, rather than to haemorrhagic causes per se (De Vries et al 1985, and see 2.6[b]). Hope et al (1988) also reported that all cases of ventricular dilatation in their postmortem series of 57 infants of gestation <33 weeks were associated with ischaemic lesions in the parenchyma.

The importance placed on IVH declined as parenchymal lesions and their sequelae were identified (see 2.6[b]). A large retrospective study by Cooke (1987) however showed a close correlation between parenchymal lesions and preceding ipsilateral IVH, suggesting a causal relationship. It was postulated that the release of vasoactive substances by thrombi in and around the ventricles may have contributed to local ischaemia and subsequently PVL. Armstrong et al (1987) suggested that isolated IVH was relatively rare, and neurological sequelae were in general due to associated white matter injury.

Thus in summary, uncomplicated IVH appears to have a good neurodevelopmental prognosis, whereas parenchymal involvement indicates a poorer prognosis. Studies examining this are described below.

2.6(b) Parenchymal Lesions

Follow up studies have confirmed the findings of Levene et al (1983a; see 2.4[a]) that a high proportion of surviving infants with cystic PVL will subsequently develop CP. Bowerman et al (1984) assessed 6 surviving preterm infants in whom ultrasound evidence of PVL had been seen in the neonatal period. All demonstrated abnormal tone, spastic diplegia being the commonest pattern, assessment being performed at between 3 and 24 months uncorrected age. McMenamin et al (1984) compared the neurodevelopmental outcome of "large" versus "small" echodensities seen on ultrasound. The authors felt that large echodensities represented haemorrhagic infarction and that small echodensities represented PVL. Eight infants with large echodensities developed porencephaly, 5 of whom were "severely" handicapped. Small echodensities were seen in 19 infants, which resolved completely in 16 cases and showed cystic degeneration in 3. Two infants showed "moderate" handicap, though the infants with cystic change were not differentiated from the rest of the group. Follow up was performed between 7 and 23

months uncorrected age.

Weindling et al (1985a) reported cystic PVL in 8% of surviving infants with a birthweight of ≤1500g. When assessed at a postnatal age of between 12 and 18 months, all showed CP and neurodevelopmental delay. Fawer et al (1985) reported that at one year of age the outcome was dependent on the size and localisation of the early lesions seen. Guzzetta et al (1986) reported the poor outcome in 75 infants with presumed periventricular haemorrhagic infarction, identified on ultrasound as intraparenchymal echodensity of >1cm. The overall mortality was 59%, with 86% of the 22 survivors assessed at follow up having major motor deficits (spastic hemiparesis or quadriparesis). A subgroup of infants with more extensive lesions had a higher mortality (81%) and all the 7 survivors had motor deficits.

All 4 infants with cystic PVL followed up by Bozynski et al (1985) developed CP, as did 8 of 10 similar surviving infants reported by Rushton et al (1985). It is important to note that 2 infants in the latter series were felt to be normal when assessed at 18 and 24 months respectively. Two out of 5 infants with "parenchymal extension" of IVH studied by De Vries et al (1985) were normal compared to the 5 infants in their series with cystic PVL, all of whom had CP. Calvert et al (1986) assessed 15 infants with PVL at ages between 5 and 39 months. Only 1 infant was normal and 8 were considered to have normal intelligence, though 5 infants were less than 9 months corrected age.

Fawer et al (1985) followed up 54 of 82 survivors of gestation ≤34 weeks to a corrected age of 1 year. Eleven infants had PVL, of whom 5 appeared normal. Only 1 infant with a normal scan was severely handicapped. The worst affected infant had both PVL and parenchymal haemorrhage. The authors noted that small cysts (2-3 mm diameter) carried a good prognosis, whereas multiple and more diffuse cystic change

correlated with a higher risk of handicap. A further report (Fawer et al 1987) in a larger cohort assessed at 18 months corrected age related the site of PVL to subsequent handicap. Frontal or focal PVL had a much better prognosis than lesions in the parietal area (half of the latter group being severely handicapped). Occipital involvement was always associated with severe handicap, including visual impairment.

In a group of 156 survivors of a cohort of 200 infants with a birthweight of <1500g, only one severely handicapped infant did not have spasticity at 18 months corrected age (Graham et al 1987). 97% of these infants with normal ultrasound scans in the neonatal period were normal neurodevelopmentally. Bilateral extensive cystic PVL was invariably associated with severe handicap, suggesting that the changes seen on ultrasound were possibly a marker for cortical injury.

Cooke (1987) reported the results of the follow up at 2 years of age or more of 524 infants with birthweights ≤1500g. CP, diagnosed in 50 infants, was strongly associated with cystic PVL and porencephalic cysts, especially if the lesions were bilateral. Some of the earlier scans in this study were reclassified at the end and the quality of imaging equipment used improved during the study period (5 years).

Stewart et al (1987) found a low probability of neurodevelopmental disorders in 342 survivors of <33 weeks gestation when assessed at between 12 and 18 months corrected age if no haemorrhage or "parenchymal echodensity" were seen on ultrasound at the age of 1 week and if the scan at the time of discharge revealed no ventricular dilatation or atrophy. Apart from the problem of being largely retrospective, this study grouped echodensity as one category and did not differentiate between the types of cystic change (ie PVL or porencephaly) later observed. The presence of ventricular enlargement or PVL on ultrasound at "term" was reported by Bozynski et al (1988) to be predictive of handicap

at 12-18 months corrected age. The number of infants in this study was relatively small (n=116), with only 3 developing PVL. Interestingly, 3 of the infants with apparently normal scans at "term" developed CP.

The outcome of infants with prolonged flare is less certain. Dubowitz et al (1985) described an infant with this appearance on ultrasound who at 18 months was severely developmentally delayed with spastic quadriplegia. Two infants assessed by Fawer et al (1987) with no cystic lesions but prolonged echodensity on ultrasound developed severe sequelae (this study also demonstrated the extremely poor prognosis of occipital cysts).

Sinha et al (1990) compared clinical events and developmental outcome between infants who developed early versus late "periventricular echodensity". Although infants from both groups developed diplegia, there was a preponderance growth retardation in infants with early onset echodensity, whereas infants who developed late echodensity had a higher incidence of IRDS. The authors postulated whether the early onset appearance might be prenatal in origin and suggested that this might be used to influence obstetric intervention.

Fawer and Calame (1991) reported the 5 year assessment of 93 surviving infants of <35 weeks gestation. Whilst confirming the association of extensive PVL and major handicap, this report also found that children whose scans had shown "small focal" areas of PVL (cystic lesions or persisting echodensity <5mm in diameter) scored lower on intellectual and psychometric testing, though the only statistically significant difference was in motor skills. Of the 51 infants with normal scans, 5 had low cognitive abilities and severe behavioural disorders.

The cohort of Graham et al (1987) was assessed at 5 years of age and the results recently reported (Levene et al 1992). Children with IVH and prolonged flare scored significantly worse on motor impairment testing than children with normal scans, but the latter group scored significantly worse than controls for both motor impairment and intelligence. Regression analysis suggested that the most important factor associated with motor impairment was low birth weight.

The clinical manifestations of such lesions may be deduced from the local neuroanatomy. The pyramidal tracts pass from the motor cortex through the internal capsule and then descend through the brainstem. The leg distribution is closer to the ventricles and is therefore more likely to be damaged, resulting in spastic diplegia. Lesions in the posterior zones are likely to involve the optic radiations, thus impairing vision.

In summary, cystic PVL would appear to be a good marker for predicting subsequent handicap, with CP being the most common finding on follow up. it is with this form of injury that the studies in this thesis will be concerned. Clearly it is important to consider factors which might predispose to PVL in an attempt to identify common pathophysiological pathways in its development.

2.7 Clinical Risk Factors for IVH and PVL

Several studies have tried to identify risk factors which predispose the immature brain to injury. idiopathic respiratory distress syndrome (iRDS)*†°, pneumothorax°, acidosis*†° and hypercapnia*†° are agreed on by several authors (Cooke et al 1981*, Levene et al 1982†, Thorburn et al 1982°) as being related to the development of PVH. More recently, Leviton et al (1989) suggested that IRDS and haemorrhage may not be causally related, since the reduction in IRDS associated with the use of artificial

surfactant therapy has not been associated with a corresponding fall in the incidence of haemorrhage. This however may reflect the change in the population of neonatal intensive care units (Field et al 1985a), the overall incidence of haemorrhage being maintained by a rise in incidence in infants of birth weight <1500g (Cooke 1991).

PVH arises due to the friability of capillaries in the germinal matrix which are maximally developed between 25 and 30 weeks gestation. They have no supporting glial membranes and the cellular organisation is loose. Many intraparenchymal vessels at this stage of gestation similarly consist of endothelial cells with little or no smooth muscle, elastin or collagen (Haruda & Blanc 1981). As these involute with increasing maturity, so the risk of PVH lessens (Trounce et al 1988). Goldstein (1979a) however contended that in general terms cerebral capillaries are resistant to rupture even under extreme experimental conditions, integrity being maintained by the basement membrane rather than by supporting cells (Goldstein 1979b). Haemorrhage would occur only if this membrane were weakened or if there was a relative deficiency of membrane as found for example in immature rats (Betz & Goldstein 1979).

Several common factors emerge from studies on risk factors for PVL. Sinha et al (1985) correlated antepartum haemorrhage (as did Weindling et al 1985b & Calvert et al 1987), asphyxia, recurrent apnoea (as did Perlman & Volpe 1985) and septicaemia with subsequent development of PVL. They hypothesised that hypotension was a common factor to all of these events, but blood pressure data was not given for this study. Support for this theory comes from animal studies (Young et al 1982) in which several manipulations with the same end result, namely hypotension, led to failure of perfusion of specific regions (periventricular white matter) with preservation of flow to others (cortical grey matter).

Whilst the idea of hypotension playing a key role in the development of PVL is very attractive, other studies in human newborns have also failed to show a positive correlation between blood pressure and PVL (Weindling et al 1985b, Trounce et al 1988). The last study did show significant independent correlation between pneumothorax and prolonged hypercapnia (>7 kPa) with PVL. Hyperbiilirubinaemia also reached statistically significant levels, though the reasons for this remain unclear.

It has also been suggested that hyperkalaemia may play a part in ischaemic cerebral injury. Edvinsson et al (1986) demonstrated that the addition of blood to cerebral arteries in vitro (hence causing a rise in the extracellular potassium concentration) produced vasoconstriction. To obtain this effect required high concentrations of potassium (15-20 $mmol.l^{-1}$) which may not occur in vivo. Similar vasoconstriction was obtained by Sasaki et al (1984) using dog basilar artery in vitro. They postulated that prostaglandins, haemoglobin and lipid hydroperoxides may all act to produce vasospasm. Stutchfield and Cooke (1989) found hyperkalaemia in the CSF of 6 out of 29 infants with IVH. Five of these infants developed cerebral infarction, although there was no specific time relation between these two events. Finally, cardiac dysrrhythmias associated with hyperkalaemia may further impair cerebral perfusion (Shortland et al 1987).

Brain metabolism may however rise in the face of impaired perfusion. The topical application of potassium over the brain in rats (Shinohara et al 1979) led to increased cortical glucose utilisation as measured by autoradiographic techniques. Haemorrhagic hypotension sufficient to cause impaired white matter perfusion in a beagle puppy model led to increased glucose utilisation in the white matter (Ment et al 1985). This model also demonstrated a rise in levels of prostaglandin E2 and the authors speculated that the uncoupling of the tissue metabolism requirements from the perfusion

may play an important role in the genesis of ischaemic injury by allowing demand for metabolites to exceed supply.

2.8 Models for the Development of PVL

Having identified a lesion associated with subsequent neurological sequelae and the clinical events which precede their onset, the next step is to identify the steps involved in the pathogenesis of these lesions. Prior to many of the clinical studies above, Wigglesworth and Pape (1978) proposed an integrated model for haemorrhagic and ischaemic lesions in neonates based on changes found in (a) the vascular supply and (b) the physiology of the developing brain observed at different gestations. Firstly, they proposed that haemorrhagic lesions resulted from increased CBF, secondary to factors such as hypoxia, hypercapnia and acidosis. Secondly, events causing decreased cerebral perfusion or vasoconstriction may result in ischaemic lesions. Both haemorrhagic and ischaemic lesions may occur in any individual at different times.

2.9 Summary

Clearly from clinical studies the pathogenesis of brain injury in the preterm infant would appear to be muitifactorial. The common final pathway in most instances seems to be via impairment of cerebral perfusion, and therefore an understanding of (a) the interrelationship of factors affecting CBF and (b) the differences between adult and preterm cerebrovascular physiology is essential in any consideration of cerebrovascular pathology. The basic patterns of cerebrovascular anatomy and the interraction of factors involoved in the control of CBF will therefore be discussed in the following chapter.

Chapter 3

The Cerebral Circulation

3.1 Introduction

The basic pattern of cerebrovascular anatomy will now be discussed followed by a summary of the evolution of theories behind regulation of the cerebral circulation. The

influence of factors including blood pressure, $PaCO_2$, arterial oxygen tension (PaO_2), autonomic innervation and vessel calibre on the cerebral circulation will be presented. In addition the effects of prematurity and aspects of neonatal intensive care (for example ventilatory modalities) on cerebral blood flow regulation will be discussed.

3.2 Blood Supply of the Developing Brain

Any studies involving preterm infants must bear in mind the changes that are occurring in all organ systems including the brain during gestation, which may alter appreciably by term. A further consideration is the major physiological adaptation that occurs in the immediate postnatal period. Although the basic pattern of the major cerebral vessels is well established by seven weeks post-conceptual age, the subsequent massive increase in size of the hemispheres of the post-embryonic fetal brain and the change in predominance from basal ganglia to cortex in the third trimester require an accompanying redistribution of the blood supply, with the internal carotid vessels becoming dominant.

Areas of particular relevance to cerebral injury in the preterm neonate are the processes of internal vascularisation (the ingrowth of blood vessels from the peripheral network to supply the developing brain) and the early predominance of the subependymal germinal matrix tissue (see 2.3).

The brain has traditionally been thought of as a hollow tube (the centre representing the ventricular system) with radially distributed arteries penetrating towards the centre. These are known as ventriculopetal vessels. Some of the basal arteries recurve from the ventricular wall in a ventriculofugal direction. This pattern of blood supply gives rise to boundary zones between ventriculopetal and ventriculofugal arteries and also between territories supplied by different ventriculopetal vessels. The position of these areas alters with maturation of the brain, which may account for the differing

patterns of cerebral injury observed at different gestations. An example of this is the finding of cortical infarcts predominantly in infants near term, due to regression of anastomoses between arterial stems (Takashima et al 1978, Trounce & Levene 1985), whereas periventricular white matter injury is almost exclusively seen in preterm infants (see 2.1).

Accompanying cortical growth in general terms there is also an increase in cortical convolutions and hence surface area. This is accompanied by an increase in metabolic activity and hence blood supply. These changes are very apparent from about 32 weeks gestation. From about 30 weeks gestation, the subependymal matrix layer thins progressively which again signifies the reduction in dominance of the basal ganglia.

In the study of infants at these gestations it must be considered that such major changes in vascular supply may well be paralleled by changes in circulatory physiology. Therefore extrapolation of data from adults or even term infants may not be justified. Animal studies have also demonstrated that even once structural evolution is complete, functional maturation of the brain is accompanied by heterogeneous changes in regional blood flow (Kennedy et al 1972). Finally, any comparative studies with animal models must consider the differences between species in the ratio of brain to total body weight and the percentage of cardiac output that the brain receives.

3.3 Cerebrovascular Anatomy (Post-embryonic)

Arterial Supply

The brain is supplied by the paired internal carotid and vertebral arteries. The internal carotid artery is a terminal branch of the common carotid. it enters the subarachnoid space by piercing the dura mater and arachnoid medial to the inner side of the anterior clinoid process. Having coursed backward below the optic nerve, it turns

upward immediately lateral to the optic chiasma, bringing it under the anterior perforated substance. At this point it divides into two terminal branches, the anterior and middle cerebral arteries, the anterior being the smaller of the two vessels.

The two anterior cerebral arteries almost meet in the midline, being joined by the anterior communicating artery. They then ascend in the longitudinal fissure and bend backwards around the genu of the corpus callosum. Branches of the anterior cerebral artery supply the medial portions of the frontal and parietal lobes and the corpus callosum.

The middle cerebral artery runs in the lateral fissure between the frontal and temporal lobes. Branches supply the sensorimotor area as well as sensory language areas in the temporal and parietal lobes.

The vertebral arteries enter the subarachnoid space at the level of the foramen magnum. They supply the cerebellum before fusing to form the basilar artery, which supplies the pons and inner ear in addition to the cerebellum before dividing into the posterior cerebral arteries. These supply temporal, parietal and occipital areas.

The major arteries supplying the cerebrum join at the base of the brain to form the circle of Willis, consisting of the anterior communicating, anterior cerebral, internal carotid, posterior communicating and posterior cerebral arteries. There is normally little exchange of blood between the main vessels. Anastomoses between branches of the anterior, middle and posterior cerebral arteries are concealed in the sulci, and there are arteriolar interconnections in the pia mater.

Venous Drainage

The cerebrum has an external and an internal venous system. The external cerebral veins lie in the subarachnoid space on all surfaces of the hemispheres, while central venous drainage occurs via the internal cerebral veins situated beneath the corpus callosum. Both sets of cerebral veins empty into dural venous sinuses. The brainstem and cerebellum drain into dural venous sinuses adjacent to the posterior fossa.

3.4 Cerebrovascular Physiology

(a) The Role of Blood Pressure

Most investigators in the nineteenth century believed that owing to the rigid nature of the skull and the three incompressible elements it contained (namely brain tissue, cerebrospinal fluid [CSF] and blood), alterations in cerebral blood volume and hence in the volume of the cranial contents could not occur. Thus CBF was said to vary directly with arterial blood pressure (ABP). This was known as the Monro-Kellie doctrine (based essentially on post mortem observations) and two of its most vociferous exponents, Bayliss and Hill wrote (1895) that the volume of blood within the brain was "...cabin'd, cribb'd, confin'd...", and thus kept constant. Many other workers of the same period were concerned to show consistency between their results and the Monro-Kellie doctrine.

This concept persisted until 1938 when Fog demonstrated the ability of the cerebral circulation to respond independently to oppose changes in ABP. Using a cranial window technique, he observed the variations in pial arteriolar diameter in response to changes in blood pressure. From this and subsequent studies using the Kety-Schmidt technique to make quantitative measurements of CBF (Kety & Schmidt 1945), it was concluded that over a range of blood pressure, changes in vessel diameter maintained a relatively constant cerebral blood flow by altering cerebrovascular resistance.

These observations gave rise to the concept of "autoregulation", which may be defined as the intrinsic tendency of an organ to maintain constant blood flow despite changes in perfusion pressure (but see beiow). Clearly at low extremes of ABP cerebral perfusion will be compromised, but within certain limits the abllity to maintain adequate cerebral blood flow over a considerable range of blood pressure has been demonstrated both in animal studies (Rapela & Green 1964, Harper 1966, Yoshida et al 1966, Strangaard et al 1974) and in man (Agnoli et al 1968, Olesen 1973). The latter two studies indicate that the degree of change in cerebral blood flow in response to blood pressure changes would appear to be extremely small. The limits of this control are presumably set by the inability of the vessels to constrict or dilate beyond a certain diameter. This may however overestimate the range over which CBF is maintained, as some animal studies have shown that the lower limit of autoregulation is reached before maximal vessel diameter is achieved (MacKenzie et al 1979).

Several factors may produce a re-settlng of the blood pressure limits for autoregulation. For example, whilst carotid baroreceptors do not influence autoreguiation (Rapeia et al 1967), chronic hypertension in adults leads to a higher upper limit of blood pressure up to which autoregulation occurs (Strandgaard et al 1973 & 1975) as the autoregulatory "curve" (blood pressure versus CBF) is shifted to the right. In contrast to this, the autoregulatory curve in term newborn animals appears to be shifted to the left (Hernandez et al 1980) and these authors suggested this merely reflects the lower range of blood pressure found in the newborn.

In preterm animals however the blood pressure range over which autoregulation occurs has been found to be narrower than in the adult and in addition the mean blood pressure was close to the lower limit of autoregulation (Papiie et ai 1985). Hypoxia has also been found to abolish autoregulation in a similar preparation (Tweed et ai 1983). it

may therefore be inferred that the preterm neonate may be more prone to cerebrovascular ischaemia under conditions of hypotension and hypoxia, as frequently occurs in association with IRDS.

It is important to note that whilst global hemispheric blood flow is maintained at a fairly constant level, there may be great variation in regional blood flow which corresponds to neuronal activity. For example, during voluntary muscle contraction in the hand, blood flow is seen to increase in the contralateral sensorimotor cortical hand area (Olesen et al 1971). The increase in neuronal activity is analogous to an increase in physical work performed by voluntary muscles and thus requires an increase in energy supply and hence blood flow. This introduces the linking of CBF to metabolic demands.

it might be expected that cerebral venous oxygen levels would remain constant despite such an increase in CBF, as there would be greater extraction of oxygen by the tissues. In fact there is an "overshoot" and cerebral venous oxygen levels increase, which suggests that oxygen is not the major factor coupling cerebral metabolism to blood flow.

Further evidence for metabolism-flow coupling comes from studies involving the administration of drugs such as barbiturates, which are known to depress cerebral metabolism and also result in reduced cerebral blood flow. This reduction occurs extremely rapidly following administration of the drug, too rapidly for it to be solely dependent on the reduction in metabolism leading to a "washout" of CO_2 with its consequent vasoconstriction and reduction of flow (see 3.4b). These observations led to the suggestion that other factors such as autonomic innervation might play a role in cerebral autoregulation (see 3.4d).

Clearly "autoregulation" is not simply a function of the responses to changes in

perfusion pressure. it may aiso be defined as the capability of an organ to regulate its blood supply in accordance with its needs. This involves the interraction of several other factors in addition to perfusion pressure on cerebrovascular resistance to maintain CBF at an adequate level to support cerebral function. The role of these other factors wiii now be discussed.

3.4(b) The Role of $PaCO_2$

(i) Historical Background

Changes in the calibre of blood vessels on the surface of the brain resulting from experimental asphyxia were first observed over 100 years ago in animal studies (Donders 1851). Despite this indication that cerebral biood vessels showed independent vasomotor activity, most investigators tried to explain such findings to show concordance with the Monro-Keliie doctrine. It was therefore greatly against the prevailing views of the time that Roy and Sherrington (1890) wrote "... the chemical products of cerebral metabolism contained in the lymph which bathes the wails of the arterioles of the brain can cause variation of the calibre of the cerebral vessels...in this re-action the brain possesses an intrinsic mechanism by which its vascular supply can be varied locally in correspondence with local variations of functional activity ...", inferring that cerebral blood flow was coupled to local metabolic requirements. Other workers were not able to reproduce Roy and Sherrington's results, and it was not until the studies of Wolff and Lennox (1930) that the "humoral" effect proposed by Roy and Sherrington was shown to be largely due to changes in $PaCO_2$ and to a lesser extent changes in PaO_2.

3.4b(ii) Methodological Considerations

Studies involving the effects of CO_2 on the circulation are beset with difficulties, most importantly involving the methods. Many reports are from studies with anaesthetised

subjects: evidence from instances where the $PaCO_2$ became inadvertently raised is obviously poorly controlled; even in controlled hypercapnia the anaesthetic agents and adjunct drugs used may themselves have profound effects on the "resting" state and subsequent responsiveness of the cardiovascular system (Cullen & Eger 1974). In addition the degree of hypercapnia induced raises considerable ethical problems. The ventilatory responses of awake subjects following administration of CO_2 may also have major effects on the circulation, mediated mechanically by mediastinal pressure changes and indirectly via baroreceptors and chemoreceptors. Associated changes in PaO_2 may also alter the degree of the CO_2 response (see 3.4c).

The use of animal models allows a greater degree of hypercapnia to be induced in addition to more invasive measurement techniques and cardiovascular manipulation, but direct comparison with humans and indeed with other animal species is difficult. Animals other than primates have different cerebrovascular anatomy, especially with regard to arterial distribution, venous drainage and the anastomoses within each system. This has particular effects on extrapolation of results to man. In addition, the experimental preparation may alter in vivo mechanisms involved in circulatory control. This is especially important in the study of the cerebral circulation if, for example, the blood-brain barrier is disrupted or the preparation is subjected to much handling or large temperature fluctuations.

The achievement of a steady state during inhalation of CO_2 is rare both in animal studies and in man, making quantitative relationships between various parameters difficult to obtain. in addition, the responses of premature neonates to both physiological and supra-physiological stimulation may differ markedly both in nature and degree from those seen at term or in the adult.

The overall haemodynamic response to a rise in $PaCO_2$ represents a balance between the effects exerted on various areas. Each individual area, for example the heart, may be affected differently when considered in isolation as opposed to in vivo with the additional effects of both neural and humoral responses. For this reason the cerebrovascular effects of CO_2 cannot be considered in isolation from systemic cardiovascular effects.

3.4b(iii) CO_2 and the Heart

CO_2 has a depressant action on isolated heart preparations, reducing both rate and force of contraction. This seems to be pH rather than $PaCO_2$ dependent, as no effect is seen if $PaCO_2$ increases whilst pH is kept constant (Price 1960). When normal men inhaled CO_2, cardiac output was seen to increase (Asmussen 1943), there being a linear relationship between the rise in $PaCO_2$ and output (Prys-Roberts et al 1967). Both direct and indirect stimulation of the sympathetic nervous system was implicated in this response, though early biological assays were not sensitive enough to detect a rise in circulating catecholamines in all experimental situations (Honig 1957). In the latter study, the importance of the autonomic nervous system was shown by the finding that inhalation of CO_2 did not result in an increase in cardiac contractile force if the spinal cord was transected; in fact a fall in force was seen, analogous to the earlier work on isolated heart preparations. The sympathetic response in rabbits could be (a) mimicked by hypothalamic stimulation, (b) reversibly blocked by spinal anaesthesia, (c) reduced and sometimes prevented by lesions within the hypothalamus and (d) abolished by removal of the adrenal glands (Cross & Silver 1962). Beta-blockade in anaesthetised dogs had a similar effect (Norman & Atkinson 1970).

3.4b(iv) Systemic Vascular Response

In general terms, the response of isolated blood vessels to an increase in $PaCO_2$ with few exceptions consists of relaxation. In the limb, an increase in $PaCO_2$ caused dilatation of the small vessels but this tended to be countered by an increase in major artery resistance in neurologically intact preparations (Fleishman et al 1957). The use of alpha-blockers such as phenoxybenzamine given intraarterially resulted in an increase In peripheral vasodilatation in response to hypercapnia (Richardson et al 1961). In the kidney a reduction in pH caused a fall in vascular resistance (Emanuel et al 1957) which was more marked in denervated preparations. Intestinal vessels showed little change or even a slight increase in resistance (Mohamed 1951), though prolonged hypercapnia led to mesenteric vasodilatation (Brickner et al 1956). These responses are thought to occur by direct action of CO_2 on vascular smooth muscle and are moderated by local neural and humoral mechanisms, the net effect being a reduction in total peripheral resistance. The pulmonary vessels tend to constrict in response to hypercapnia, and it has been suggested that this is due to an intrinsic mechanism which normally shunts blood away from poorly ventilated areas.

3.4b(v) Cerebrovascular Response

Whilst the effect of CO_2 on the cerebral vessels is readily observed, the mechanisms responsible are complex. There has been much debate as to the relative involvement of local metabolic, humoral and neurogenic influences on the control of the cerebral circulation both as a whole and locally, and the mechanism by which CO_2 exerts its effects has also been the subject of great controversy.

Studies by Shalit et al in anaesthetised dogs (1967 a,b,c) suggested the following. Firstly, a neural reflex mechanism responsive to CO_2 existed for CBF regulation; this was

based on the finding that infusion of CO_2 into the subarachnoid space caused a rise in cerebral blood flow, without a rise in arterial or venous CO_2 tension. In addition, acidification of the cerebrospinal fluid (CSF) with ammonium chloride did not lead to an increase in blood flow. Secondly, they demonstrated that an increase in cerebral perfusion rate occurred with a rise in systemic CO_2 tension but not to local infusion of CO_2 into a branch of the middle cerebral artery, which in fact constricted. They felt that this indicated that the effect of CO_2 on the cerebral circulation was not mediated by direct action on vascular smooth muscle, but the effects on smaller vessels were not studied. Finally, destruction of the high medulla, pons and mesencephalon both reduced CBF and reduced the responsiveness of the cerebral circulation to CO_2. Sectioning of the brainstem rostral but not caudal to the pontomedullary junction (Capon 1975) abolished the cerebrovascular response to CO_2, supporting the possibility of a CO_2 responsive centre in the brainstem. It must be noted at this point that all the above procedures were extremely invasive and the preparations of Shalit et al did not exhibit autoregulation, which casts doubt as to their representation of the situation in vivo.

A local "brain-tissue CO_2 tension" effect was implicated by Shapiro et al (1965), based on the response time of CBF to an increase in $PaCO_2$. Severinghaus and Lassen (1967) and Skinhøj and Paulson (1969) suggested that either pH or CO_2 itself acted directly on blood vessel walls. In the latter study, the infusion of hypercapnic blood into the vertebral arteries had no effect on blood flow in the frontal and parietal regions, but did increase cerebellar blood flow. Infusing the same blood into the carotid arteries increased blood flow in the former areas. This made the possibility of a brainstem centre which directly controls CBF unlikely; as to whether CO_2 or pH acted directly on vascular smooth muscle or through pH changes in the extracellular fluid was not addressed.

Acetazolamide, which blocks the formation of hydrogen ions by carbonic anhydrase abolishes the vasodilator response to CO_2. The studies by Raper et al (1971) showed that smaller pial vessels dilated more than larger ones to a given rise in $PaCO_2$ and the time constant observed was again in favour of an extracellular fluid change. Prolonged hypocapnia in anaesthetised dogs and awake human volunteers resulted in a fall in cerebral blood flow followed by a gradual rise towards control levels, again suggesting that control over cerebral vessels is mediated via changes in interstitial fluid pH (Ralchle et al 1970). interestingly, the control animals in this study showed a gradual fall in CBF over a period of hours and this may explain some of the conflicting results in this area.

Perfusing the space under cranial windows in cats with mock CSF containing varying CO_2 tensions allowed the indirect effect of CO_2 on pial arteries to be demonstrated. Increasing CO_2 tensions and falling pH levels caused proportionate vessel diameter increases. Microapplication of CSF of various pH values caused pial dilatation within seconds, the degree of dilatation being inversely proportional to the pH of the applied fluid (Kuschinsky et al 1972). If the pH is kept constant as the CO_2 tension increases, no response is seen (Kontos et al 1977). It has also been shown however that the vasoconstrictor effects of noradrenaline on pial vessels work better in an alkaline environment (Wahl et al 1972). The failure of blood containing lactic acid or bicarbonate to alter CBF probably results from differential permeability of the blood-brain barrier (Mchedlishvili 1986). It is possible however, that there may be a brainstem system which sensitises vascular smooth muscle to the effects of CO_2. it is likely to be part of the ascending reticular activating system and may be a monoaminergic ascending pathway. This is supported by the fact that barbiturates reduce CO_2 reactivity (Fujishima et al 1971, Grubb et al 1974).

The role of prostaglandins in cerebrovascular regulation is uncertain. Using a cranial window technique in cats, Wei et al (1980a) inhibited prostaglandin-Induced pial dilatation with indomethacin and another similar agent. The cerebrovascular response to CO_2 was unimpaired, though this may have been a result of the pH of the vehicle used for the applied drugs, since using a similar technique in newborn pigs, Wagerle and Mishra (1988) suggested that vasoactive prostaglandins did have a role in mediating the CO_2 response. The response was also abolished by indomethacin in preterm infants (Edwards et al 1990) as well as in rats (Dahlgren et al 1981) and gerbils (Crockard et al 1982), but not in rabbits (Busija 1983).

The cerebrovascular sensitivity to $PaCO_2$ appears to be mainly a local and intrinsic phenomenon, an increase leading to a fall in cerebrovascular resistance and consequently a rise in cerebral blood flow. In addition, since regional cerebral blood flow is tightly coupled to metabolism it would be expected that the hyperventilation seen in response to hypercapnia would be associated with an increase in metabolism and hence blood flow in the medullary respiratory centre: this does not occur.

3.4b(vi) CBF/CO_2 Relationship

The development of a reliable method of measuring cerebral blood flow (CBF) by nitrous oxide inhalation (Kety & Schmidt 1945) enabled its rise during hypercapnia to be quantified. The relationship between increase in $PaCO_2$ and CBF in humans has been reported as both linear (Shapiro et al 1965, Grubb et al 1974, Alberti et al 1975) and exponential (Kety & Schmidt 1948, Olesen et al 1971, Tominaga et al 1974).

The degree of response has been suggested to depend firstly on the baseline CBF, presumably related to the inability of the cerebral vessels to either dilate or constrict

beyond a certain point (Grubb et al 1974). In addition, the buffer capacity of the brain extracellular fluid (ECF) may also influence the CO_2 response, since the latter appears to be mediated by pH. The ECF contains little protein or other non-bicarbonate buffers and its buffer capacity to CO_2 is therefore low and dependent on the amount of bicarbonate present. Elevation of the ECF bicarbonate concentration as seen in respiratory acidosis and metabolic alkalosis will attenuate the change in ECF pH with a rise in CO_2 tension and thus affect the subsequent vascular response. A fall in ECF bicarbonate concentration will produce the opposite effect.

Arterial pathology may also affect the degree of CO_2 reactivity. In adults, the responsiveness of the cerebral vasculature to a rise in $PaCO_2$ is attenuated in the presence of arterial disease (Bullock et al 1985). Surgical revascularisation results in restoration of the degree of response (Bishop et al 1987).

The influence of the cerebrovascular innervation on the response to CO_2 has been variably reported by different authors. The impaired response reported by James et al (1969) following cervical sympathetic stimulation may have been due to the method of preparation and also to repetitive stimulation.

Kobayashi et al (1971) observed dissociation between cerebral blood flow changes in response to CO_2 and measured calibre changes in larger pial vessels (50-250 μm) before, during and after cervical sympathetic stimulation. This suggested a differential response dependent on vessel size. Sercombe et al (1975) compared the response in rabbits in the caudate with that of the lateral geniculate body to both CO_2 and a variety of catecholamines and concluded that the response was dependent on the degree of

innervation, though the use of chronically-implanted electrodes to measure cerebral blood flow by heat clearance in this study has been criticised (see 3.4d).

Larger vessels are more densely innervated than smaller ones and the smaller response to hypercapnia seen in the former using a cranial window technique is postulated to reflect their degree of innervation (Wei et al 1980b). The application of phentolamine topically or ipsilateral cervical sympathectomy produced an equal response from all vessel sizes. No increase in baseline blood flow was seen following either of these procedures at normocapnia, which the authors felt indicated low resting vasoconstrictor tone in the preparation.

The roles of the carotid body and sinus have likewise been the subject of some debate, again with conflicting results claimed by several authors. Ponte and Purves (1974) recorded a greatly reduced cerebrovascular response to hypercapnia and hypoxia following section of the carotid sinus nerves, in addition to pressure passive blood flow. Their preparation did however require a great deal of surgical preparation. Using a well-validated microsphere technique to measure cerebral blood flow, McCalden & Rosendorff (1977) found no significant changes following denervation of the carotid body and attenuation of CO_2 responsiveness only at extremely high CO_2 tensions. This tends to suggest a relatively unimportant role, at least under normal physiological conditions.

The cerebrovascular response to CO_2 could be enhanced by infusion of the cholinesterase inhibitor neostigmine (Aoyagi et al 1975) and attenuated by infusion of atropine (Kawamura et al 1975) into the vertebral arteries in baboons. No such effect was obtained by the same infusions into the internal carotid arteries, which suggested a central cholinergic system with a vasodilator influence, located in the brainstem or diencephalon.

The blunted cerebrovascular response to CO_2 in several immature animal species (Reivich 1964, Reivich et al 1972, Shapiro et al 1977, Hernandez et al 1978) is thought not to be related to metabolic demands but to vascular maturity and density (Rosenberg et al 1982). This has not been found in premature infants (Leahy et al 1980, Greisen & Trojaborg 1987, Levene et al 1988).

Attenuation of the response occurred with hypotension (Harper & Glass 1965, Grubb et al 1974) and chronic hypercapnia (Pannier & Leusen 1973). Neither the haematocrit, which was inversely related to the blood flow velocity (Wade 1981) nor the resting blood pressure affected the degree of response to CO_2 (Tominaga et al 1974). Regional CBF studies have shown an increased responsiveness in more caudal brain structures (Ashwal et al 1984, Hansen et al 1984, Brubakk et al 1987).

3.4(c) The role of PaO_2.

Changes in PaO_2 on the cerebral circulation as part of an asphyxiai insult were observed by Donders (1851), but Wolff and Lennox (1930) were the first to study the effects of hypoxia separately from hypercapnia. The main finding of their work was that the cerebral vessels were more sensitive to changes in $PaCO_2$ than changes in PaO_2. Hypoxia was shown to cause vasodilatation and hyperoxia to cause vasoconstriction. Human studies (Shapiro et al 1966) demonstrated that hypoxia acts additively with hypercapnia in causing a rise in cerebral blood flow, but Quint et al (1980) showed that the level of hypoxia (in rabbits) had to be <6.7 kPa for this additive effect to occur. Combined hypoxia and hypercapnia also acts synergistically on the catecholamine response (Rose et al 1983).

The cerebral arteriolar vasoconstriction induced by hyperoxia has been shown to change quantitatively with maturity. Kennedy et al (1971) found the vasoconstriction to be more marked in the first few days after birth in puppies compared to similar studies performed at 3 weeks of age. The greater response to hyperoxia found in term as compared to preterm infants by Nijima et al (1988) was probably due to the concurrent fall in $PaCO_2$.

3.4(d) The Role of Autonomic Innervation

The presence of nerve fibres on the anterior and posterior cerebral arteries were first described over 300 years ago (Willis 1664). It has been subsequently shown that there is a rich innervation of the pial vessels in both a variety of animals and in man, the arteries being more densely supplied than the veins. There are however conflicting opinions on the importance of neurogenic influence on the cerebral circulation.

The presence of sympathetic adrenergic fibres originating from the ipsllateral superior cervical ganglion has been demonstrated by denervation studies which lead to the disappearance of transmitter substance from the tissue. The amine mechanisms demonstrated in human brain vessels (both embryological and adult) appear to be principally the same as those shown in greater detail in animal studies (Edvinnson et al 1976).

The cholinergic distribution has been shown to follow that of the sympathetic closely (Iwayama et al 1970) and in addition transmitters such as noradrenaline, adrenaline, dopamine, indolamine and histamine are thought to act in a "central amine" neurone system (Edvinnson & Mackenzie 1976). Vasodilatory peptides found in other areas of the body, such as vasoactive intestinal peptide, have also been identified in the brain (Larsson et al 1976). This abundance of innervation has resulted in a multitude of

studies involving both stimulation and denervation in attempts to define the role of the autonomic nervous system in cerebrovascular regulation.

The infusion of amines both intraarterially and intravenously leads to a variety of effects in different species. Noradrenaline and adrenaline have been shown to cause a rise, a fall and no change in cerebral blood flow, a fall being the most common (Edvinsson & MacKenzie 1976). Such results using microapplication techniques (Wahl et al 1972) have not been achieved consistently by other groups using identical methods and paying particular regard to the pH of the applied fluid. In addition the concentrations of noradrenaline needed for vasoconstriction were vastly supraphysiological (Wei et al 1975). The reduction in flow thus achieved is generally relatively small, being up to 20% in studies where the total flow is measured. These changes are not readily detected by many of the techniques employed to measure cerebral blood flow. in addition, the artery selected In different species may profoundly affect where the agent infused reaches.

The infusion of either adrenaline, noradrenaline or angiotensin into the internal carotid artery in man resulted in no change in cerebral blood flow, and any changes in cerebrovascular resistance were secondary to alterations in blood pressure (Olesen 1972). This was supported by Hobson et al, studying several adrenergic agonists in the baboon (1975). They concluded that no effect on the cerebral circulation occurred without accompanying cardiovascular changes.

In contrast to this was the cephalic (external carotid) circulation, which did manifest blood flow changes without corresponding alterations in blood pressure. Amines given in this manner however may have limited access to cerebrovascular smooth muscle because of the blood-brain barrier. Topical application of catecholamines produced no response in pial precapillary vessels (Raper et al 1974), though this may have been

influenced by the pH of the applied fluid.

Similarly, the effects of alpha-blockers (Skinhøj 1972, Meyer et al 1973) and beta-blockers (Aoyagi et al 1975) are conflicting. Alpha-blockers lower blood pressure and beta-blockers reduce cerebral metabolism. For these reasons, Oishi et al (1979) chose to study the effects of blocking dopamine beta hydroxylase, which is the final enzyme in the pathway producing noradrenaline. Using this method resulted in a significant increase in cerebral blood flow without a concomitant rise in blood pressure, suggesting that the sympathetic nervous system has a role in maintaining the resting tone of the cerebral vessels. This vasodilatation was not due to the acidity of the agent used, as infusion of a solution of identical pH had no effect. A direct vasodilator of the agent itself could not be ruled out.

The results of stimulating or sectioning the cervical sympathetic chain have aroused much controversy over methodological validity and even in their interpretation. The methodological problems may be divided into intrinsic and technical.

Intrinsic problems to the cerebral vasculature include "contamination" of intracranial with extracranlal blood, changes in cerebral metabolism resulting from the experimental procedures, variability of regional vascular responses and species differences. Technical problems include trauma, leading to loss of autoregulation, inadequate control of blood gases and blood pressure and variations in conscious level.

Using an in vitro preparation, Lee et al (1976) showed that the alpha-adrenergic receptors in rabbit basilar artery were relatively insensitive to transmural nerve stimulation compared to those in other vascular beds. In addition, they were not blocked by conventional alpha-blockers, for example phentolamine. This suggested that despite

the dense innervation of the cerebral vasculature the nerves themselves did not behave in a typical manner.

In vivo, using an anaesthetised dog model, Traystman and Rapela (1975) found effect on the cerebral vasculature from stimulation of the stellate ganglion. In a similar preparation, Heistad et al (1977) found minimal neural influence on the cerebral vasculature except in severe hypertension. This study used the contralateral cerebral hemisphere as a control to compare the effects of both cervical sympathetic stimulation and section. The preparation also exhibited the normal pupillary response to cervical stimulation and the cerebral vasculature responded appropriately to hypocapnia. These workers speculated that the sympathetic vasoconstriction seen in acute severe hypertension may protect the blood-brain barrier from disruption.

Similar studies involving either stimulation or sectioning of nerves thought to carry parasympathetic fibres have led to conflicting reports. Ponte and Purves (1974) found an increase in cerebral blood flow in response to carotid body stimulation which could be abolished by sectioning the facial nerve. They also claimed that regional cerebral blood flow was inversely related to carotid sinus pressure. Others failed to show effects either on resting cerebral blood flow or on the responses to hypercapnia and hypoxia from similar procedures (Busija & Heistad 1981).

Injection of atropine into the vertebral arteries had no effect on cerebrovascular autoregulation, but did affect the response to CO_2, suggesting the presence of cholinergic fibres in the brainstem or diencephalon with a vasodilatory action (Kawamura et al 1975). As with the sympathetic system, the cholinergic innervation may only serve a function under exceptional circumstances.

Several groups however have shown significant sympathetic adrenergic influence. Cervical sympathectomy in the baboon was followed by a rise in cerebral blood flow and cervical stimulation caused a reduction in flow (James et al 1969). In addition, sympathectomy was followed by an increased cerebrovascular responsiveness to CO_2. Harper et al (1972) confirmed the rise in cerebral blood flow following cervical sympathectomy, but the fall in flow on cervical sympathetic stimulation was not found to be significant except during hypercapnia.

This group formulated the "Dual Effects" hypothesis which postulated that the cerebral circulation acted as two resistances in series. First are the intraparenchymal vessels, which are regulated by local metabolic effects. The extraparenchymal vessels have a degree of autonomic control, with the plal vessels being "transitional" and possibly influenced by both local and neural factors. Should the intraparenchymal vessels be dilated secondary to hypercapnia, for example, sympathetic stimulation of the extraparenchymal vessels will cause vasoconstriction and thus potentiate a fall in total cerebral blood flow.

Support for this hypothesis came from the work of Fitch et al (1975), who demonstrated that acute cervical sympathectomy or alpha-blockade enhanced the maintenance of cerebral blood flow in the face of graded haemorrhage. Chronic unilateral cervical sympathectomy resulted in a significant reduction in noradrenergic innervation of the ipsilateral extraparenchymal vessels (Hernandez-Perez et al 1975).

The major criticisms that have been made of studies supporting the role of the autonomic nervous system in cerebrovascular autoregulatlon are as follows. Firstly, the animal model used may have profound effects on the interpretation of cerebral blood flow results, due to connections between the intracranial and extracranial circulations.

Secondly, the rate of injection of inert tracers is crucial and different species display different tracer washout kinetics. Many of the studies are not validated by work using radio-labelled microspheres to measure cerebral blood flow in response to cervical sympathetic stimulation (Meyer et al 1977). The chronic insertion of electrodes to measure cerebral blood flow by heat clearance may disrupt the blood-brain barrier (Heistad & Marcus 1978). This technique may be influenced by capillary surface area which may be altered by neural stimulation with little effect on total blood flow. Finally, the degree of plal arteriolar diameter change seen in several studies (7% - Wei et al 1975; 12% - Kuschinsky & Wahl 1975) probably have minimal effects on blood flow.

In summary, although various studies have demonstrated that cerebral blood vessels have the capacity to respond to adrenergic stimulation, they do not prove that such a capacity subserves an important physiological function under normal conditions. It may however be of use in situations where normal regulatory limits have been reached (Berntman et al 1979) or (in the extreme preterm situation) if normal regulatory mechanisms have not been fuliy established.

3.4(e) The Role of Vessel Calibre

The relative role of the large and small vessels in regulation of cerebral blood flow is also the subject of much controversy. Extrapolation of experimental animal data to man figures extensively in the literature. Many animal studies have employed variations of the cranial window technique to make direct observations of the responses of pial arteries and arterioles.

There are several potential sources of error inherent in this technique. Any contamination of the field may result in vasoconstriction, which will cause an overestimation of any pressure drop across the pial bed. In addition, the branching

pattern of the surface vessels is very variable, as are the anastomoses, leading to parallel blood flow and resistance pathways, necessitating multiple measurements to be made.

Using such techniques to measure pial arteriole pressure, Shapiro et al (1971) recorded a 40% loss of aortic pressure proximal to the pial microcirculation (200-450 μm), suggesting a major role for the larger vessels. This was supported by Heistad et al (1978), but the technique used by this group relied on measuring the pressure gradient across the circle of WIIIIs following occlusion of the vertebral artery by the pressure-measuring catheter. Stromberg et al (1972), again using a micropipette technique, showed that the effect of larger vessels on cerebrovascular resistance diminished with increasing blood pressure, whereas the influence of the smaller vessels increased.

Busija et al (1981) used a more sophisticated cranial window technique incorporating an in-situ Doppler probe to measure cerebral blood flow velocity (CBFV) and an electronic micrometer to assess arteriolar size. Good correlation of cerebral blood flow was found with this method compared to labelled microspheres. They found that the response to hypocapnia consisted of arteriolar constriction with no change in CBFV, which they took to indicate that similar diameter changes were occurring at all levels of the cerebral circulation.

Hypercapnia on the other hand produced both an increase in arteriolar diameter and a rise in velocity, from which it was concluded that the degree of vasodilatation in more proximal (ie larger) vessels must be greater. The degree of hyper- and hypocapnia induced were not standardised however, and the hypercapnic groups had a non-uniform blood pressure response. No control group was used to observe alterations in CBFV with time (Raichle et al 1970).

Kobari et al (1987) used a cranial window technique which combined Doppler studies of pial arterioles combined with measurement of vessel calibre. They studied the effects of graded hypotension and hypercapnia and observed the preferential effects on smaller vessels as found by Wei et al previously (1980b). From the changes in vessel diameter, CBFV and mean blood pressure they concluded that the main site of regulation of cerebral blood flow in response to alterations in $PaCO_2$ and blood pressure was at the level of the small pial arterioles. The results of other studies (Mchediishvili 1986) give further support for major (intracerebral) arteries not being involved in the response to hypercapnia.

3.5 Specific Problems of the Preterm Neonate

The transition from intrauterine to independent life requires many major physiological changes, most notably in the cardiovascular and respiratory systems. The elimination of the umbilico-placental circulation and the closure of vascular shunts at birth dramatically alter the haemodynamics of the circulation. In particular, the umbilico-placental circulation tends to dampen the reactivity of the fetal circulation to the effects of vasoactive agents, and thus after birth the circulatory response to both physiological and pathological stress is enhanced. The ability of the brain and other organs to regulate their blood flow depending on their metabolic requirements during this changeover period is essential to the maintenance of normal function.

Wigglesworth and Pape's model for cerebral injury in the preterm neonate (see 2.4) has prompted many studies directed at elucidating the sequence of events which result in neurodevelopmental injury. The majority of this work has been directed at examining circulatory parameters, in particular blood pressure and cerebral blood flow and relating these to subsequent outcome. Certain clinical events (see 2.3) appear to be associated with a poor neurodevelopmental outcome, but in most cases a direct causal link has not

been established, although many such events have the common effect of compromising systemic blood pressure. It may also be important to consider whether any injury results from prematurity itself (and the reasons for preterm delivery) or from side effects of neonatal intensive care.

Lou et al demonstrated that asphyxia caused failure of fetal cerebrovascular autoregulation in experimental animals (1979a) and human neonates (1977 and 1979b), though the latter studies were not in well-defined populations and had heterogeneous clinical problems. In addition the high $PaCO_2$ levels in the premature infants studied may have caused maximal cerebrovascular dilatation already, and thus they could not respond further to changes in cerebral perfusion pressure secondary to hypotension.

The presence of an absolute cerebral blood flow of less than 20 ml/100g/minute as measured by ^{133}Xe clearance in the first few hours after birth appeared to be correlated with an abnormal neurodevelopmental outcome and cerebral atrophy (Lou et al 1979c).

Sick preterm infants are more likely to develop patent ductus arteriosus ([PDA]; Danilowicz et al 1966) which may have profound effects both on systemic and on cerebrovascular haemodynamics. The presence of a PDA is associated with a high left ventricular output (Alverson et al 1983). Preterm lambs have the ability to increase their cardiac output by up to 100% in the presence of a PDA (Clyman et al 1987) but this is at the expense of a redistribution of blood away from the lower body. This increase in cardiac output is achieved in part by an increase in left ventricular stroke volume, which also occurs in preterm infants provided ventricular afterload is low. Such a situation is possible in the transitional neonatal circulation, with falling pulmonary resistance and ductal patency.

With regard to the cerebral circulation, Perlman and Volpe (1981) demonstrated a rise in Doppler pulsatility index which they attributed to a fall in cerebral diastolic flow velocity in infants with a proven PDA. This may have resulted from one of two possible mechanisms.

Firstly, there may have been a failure of the cerebral vasculature to further dilate in the face of altered flow thus reducing resistance and restoring flow. Alternatively, the cerebral vasculature may have been maximally dilated already, and indeed the infants with PDA had higher $PaCO_2$ levels than their controls. They postulated that this ductal "steal" may be important in the pathogenesis of neurological injury, be it ischaemic or haemorrhagic. Retrograde diastolic flow was also found in the cerebral arteries by Martin et al (1982) and this flow pattern normalised after ductal closure.

Evidence against cerebral ischaemia being produced by ductal shunting is as follows. in diastole there is a large retrograde flow of blood in the aorta below a PDA (Serwer et al 1980). Rudolph et al (1964) showed an increase in mean flow in the ascending aorta and brachiocephalic artery in dogs with experimental aortopulmonary shunts and Spach et al (1980) demonstrated the maintenance of cerebral blood flow in infants and older children at the expense of the lower body.

In addition to these major physiological disturbances, other relatively minor considerations may influence patterns of cerebral blood flow. Whilst the effects of raised intracranial pressure on cerebral blood flow seen in experimental animals due to a rigid cranium (Leech & Miller 1974) may not be extrapolated to the neonatal situation, the more malleable neonatal skull may engender its own problems. Overlapping of the parietal and occipital bones secondary to positioning of the infant's head may compress the superior sagittal sinus, reducing blood flow and thus raising intracranial venous pressure

(Newton & Gooding 1975). This will in turn reduce cerebral perfusion pressure.

Healthy term infants show a wide variation in blood velocity in the superior sagittal sinus (measured by Doppler) with position (Cowan & Thoresen 1985). This was most marked with rotational movements through 90°. The range of movements studied encompassed all the "normal" changes in posture a baby would encounter with day to day handling, with no obvious deleterious consequences, but similar movements in a critically sick preterm infant may be less well tolerated. Similarly, brief (2-3 seconds) bilateral pressure over the jugular veins resulted in an immediate fall in blood flow velocity in the vein of Galen (Fenton et al 1991).

Hypercapnia has been implicated in the aetiology of both periventricular haemorrhage and leukomalacia (see 2.3). Hypocapnia on the other hand has been suggested to possibly reduce the incidence of IVH (Lou et al 1982). $PaCO_2$ levels below the normal range however may be associated with neurological sequelae, manifested in one report as both diplegia and dystonia in the absence of abnormalities on ultrasound (Greisen et al 1986).

The early emphasis placed on IVH in the pathogenesis of neurological injury led to a number of studies looking at the aetiological role of circulatory volume expansion. Experimental hypertension and rapid volume replacement following induced hypovolaemia in animal models (Goddard et al 1980 and 1982) and rapid volume expansion in human neonates (Goldberg et al 1980) were associated with an increased incidence of IVH. Milligan (1980) reported iVH within 12 hours of either replacement or exchange transfusion in 5 extremely sick premature infants. Four of them died shortly afterwards suggesting that other factors may have been involved. Similar results have not been achieved in other animal models (Laptook et al 1982).

Since oxygen delivery to the tissues is crucial to normal metabolism, it has been postulated that haematocrit may affect perfusion in this way in addition to viscosity effects. Fan et al (1980) varied the haematocrit in dogs isovolaemically and found an increase in blood flow to brain and myocardium at low haematocrit out of proportion to the concurrent increase in cardiac output. A high haematocrit resulted in cerebral and myocardial vasodilatation to maintain a constant oxygen supply. This effect was less marked in other organs.

3.6 Problems Related to Neonatal Intensive Care

The major impact of neonatal intensive care in improving mortality rates in preterm infants was to a great extent a result of the introduction and early use of ventilation techniques as recommended by Reynolds (1971) and others (Herman and Reynolds 1973). This particular advance was not without problems of its own, with both short- and long-term sequelae of barotrauma. The circulation may be compromised by major respiratory complications such as pneumothorax, but in addition each ventilatory parameter may at their extremes also result in similar circulatory compromise. This compromise essentially occurs secondary to either reduced venous return or reduced ventricular output and are discussed further in chapter 6. Another consideration in this area is the effects of the infant's interraction with the ventilator and its modification by the use of paralysing agents such as pancuronium.

Intubation and mechanical ventilation necessitate the use of suctioning to maintain patency of the endotracheal tube. This procedure has been found to result in a rise in blood pressure, cerebral blood flow and intracranial pressure (Perlman & Volpe 1983) but this may reflect a combination of the effects of hypoxia and noxious stimulation rather than demonstrating a lack of cerebrovascular autoregulation. Perlman and Volpe have also implicated the fall in CBFV associated with apnoea and bradycardias with the subsequent

development of PVL (1985).

Mechanical ventilation has also been shown to increase cranial blood volume (Milligan et al 1981) compared to spontaneously breathing infants (Leahy et al 1982). This effect is dependent on the stage of the infant's lung disease, as it occurs more at higher lung compliances (ie in relatively less severe disease).

3.7 Summary

Cerebral blood flow (at least in adults) appears to be closely linked to metabolism and can be greatly influenced by local "environmental" changes, in particular changes in $PaCO_2$. The rapid response to fluctuations in perfusion pressure also ensure relatively small changes in blood flow. Under normal conditions, the role of factors such as the autonomic nervous system and circulating catecholamines and prostaglandins appears to be relatively minor. Factors related to (a) prematurity and in particular the need for mechanical ventilation and (b) the transitional nature of the neonatal circulation may compromise the integrity of cerebrovascular regulation in sick preterm infants. The next question to address is the method to be used for studying changes in CBF, and this will be discussed next.

Chapter 4

Measurement of Cerebral Blood Flow

4.1 Introduction

Investigators were attempting to study the regulatory mechanisms of the cerebral circulation well before accurate methods of measuring blood flow were available. It was realised that the pulsations of the brain were arterial in origin (Ridley 1702) and the end of the nineteenth century saw attempts to measure blood flow through skull defects in dogs (Roy & Sherrington 1890) and in man (Mosso 1881).

From the discussion in chapter 3, it can be seen that the control of CBF is extremely complex and is influenced by many inter-related physiological variables. In addition, there are considerable regional differences in flow and therefore any method of assessing CBF will only give a crude overall estimation. In choosing a method for measurement of CBF there is a need to consider: (1) safety, (2) clinical applicability,

(3) quantitative performance and (4) the actual physiological or clinical questions being asked. Ideally the method used should allow continuous measurement, since the clinical situation and physiological variables which influence CBF change constantly. The following techniques have been used in the assessment of CBF in neonates.

4.2 Measurement of Cerebral Blood Flow

(a) Kety-Schmidt Technique

This method is based on the Fick principle and uses the inhalation of low concentrations of nitrous oxide (N_2O) as an inert, diffusible tracer. Intermittent sampling of arterial and cerebral venous blood is performed whilst the subject inhales N_2O until a steady-state saturation is achieved. Arterial and venous N_2O concentrations are plotted against time and cerebral blood flow is calculated from:

$$CBF = \frac{(I_v)_t \cdot \lambda}{\int_0^t (I_a - I_v)\, dt} \qquad [1]$$

where $(I_v)_t$ is the N_2O concentration at equilibrium, λ is the blood brain partition coefficient and the integral is effectively the area between the arterial and venous saturation curves.

This method has been used in children (Baird & Garfunkel 1952) and in three term infants with CNS malformations (Garfunkel et al 1954). It is however impractical for repeated use in neonates for several reasons:

(1) It is invasive requiring both arterial and jugular venous sampling.

(2) It is assumed that all areas of the brain are equally well-perfused and are thus equally saturated with N_2O.

(3) CBF estimations obtained in this way represent a mean flow over the period allowed for equilibration for the area drained by the jugular vein (which may include some extracerebral blood).

(4) There is a possibility of counter-current exchange of N_2O from artery to vein, effectively increasing the difference between tissue and venous concentrations.

(5) The method is affected by right to left shunts.

(6) The partition coefficient varies between individuals even of the same gestation.

4.2(b) Radio-labelled Xenon Clearance

This method is also based on the Fick principle, and the results obtained are similar to those using the Kety-Schmidt technique. ^{133}Xenon is used as the inert tracer and gamma cameras around the head are used to detect tissue concentrations rather than using blood sampling. The tissue concentration at any time is assumed to be proportional to the concentration in venous blood, the relationship being expressed by the blood-brain partition coefficient. Since Xenon is highly lipophilic the blood-brain partition coefficient is dependent on the degree of myelination, which may vary significantly between individuals even of the same gestation. ^{133}Xenon estimation of CBF in neonates has been performed by intra-arterial (Lou et al 1977), Inhalation (Ment et al 1981) and intravenous administration (Younkin et al 1982, Greisen 1986). Each method has disadvantages (in addition to the common problem of using a source of ionising radiation as a tracer) which will be summarised below.

Intra-arterial ^{133}Xenon clearance requires the use of an umbilical arterial catheter which is manoeuvred to the root of the left carotid artery before injecting a bolus of tracer in normal saline. Xenon clearance is monitored over the first 60 seconds after

injection, which represents flow only to the most richly perfused parts of the brain. Due to the site of injection, blood flow to extracerebral structures via the external carotid artery is included in measurements, though this is thought to have little effect on clearance over the first minute after injection.

The inhalational technique requires the use of a larger amount of tracer (approximately 10 times that required for the intra-arterial method). Unlike in the former method, the arterial Xenon concentration does not fall to zero after stopping inhalation due to the large amount used and the uptake of tracer into all tissues. This problem may be overcome by assuming equilibration of pulmonary capillary blood with alveolar air, enabiing an estimation of arterial Xenon concentration from gamma emissions over the chest. However this in turn will include emissions from the chest wall as well as the lungs, resulting in an overestimation of arterial concentration. In addition, gamma emissions over the head will include Compton scatter from Xenon in the airways, resulting in an overestimation in clearance rate.

Intravenous administration of ^{133}Xenon also uses gamma emissions over the chest to estimate arterial Xenon concentrations, though this may result in underestimation in the presence of right-to-left shunting. Late release of ^{133}Xenon from perivenous tissues will result in an underestimation of CBF. As with the inhalatlonal method, care has to be taken to remove exhaled Xenon from the measurement field.

4.2(c) Venous Occlusion Plethysmography

This technique measures the rate of increase in volume of a limb or part following occlusion of the venous outflow. The principle of volume plethysmography was first described by Schafer and Moore (1896) and was subsequently adapted to estimate human limb blood flow by Hewlett and Zwaluwenburg (1909). A rigid, fluid-filled jacket

encased the limb and thus changes in limb volume displaced fluid from the jacket, allowing estimation of changes in blood volume. This rather cumbersome method was modified by Whitney (1953). He used mercury-in-rubber strain guages to measure the percentage change in limb girth and from this determined the percentage change in volume.

Cross et al (1976) applied this method to estimation of cranial blood flow in the newborn. Bilateral compression of the jugular veins results in a stepwise increase in occipito-frontal circumference with each heartbeat. This increase slows and reaches a plateau as the increase in intracranial pressure allows non-jugular venous outflow to increase (see below) and equal arterial inflow (which may decrease). Quantitative assessment of CBF may be achieved either from the increase in head circumference during the first heartbeat (Cooke et al 1977) or by fitting an exponential term to an extrapolated increase in circumference over several beats (Cross et al 1979). Venous occlusion plethysmography has been used fairly extensively to study the effects on CBF of sleep states (Milligan 1979) and feeding (Dear 1980, Rahilly 1980), as well as to examine the relationship of arterial blood pressure to CBF in sick (Milligan 1980) and in healthy infants (Mukhtar et al 1982).

There are several potential sources of error with this technique. For it to be accurate, it is essential that the part under study must expand freely during venous occlusion. Sustained jugular venous occlusion however leads to a progressive rise in cerebral venous and intracranial pressures (see above) and the arterial inflow therefore decreases. Under normal conditions approximately 5% of the cerebral inflow leaves through the vertebral veins and this proportion increases with jugular venous occlusion. The effects of incomplete or variable jugular compression as well as unintentional carotid occlusion must also be considered. In addition the compliance of the skull has a limiting influence on the rate of skull expansion and this expansion is not uniform in all directions.

Increases in skull volume secondary to raised intracranial pressure due to for example crying and wrinkling of the skin under the strain gauge will cause errors in measurement with this technique. Also included in measurements will be extracranial flow. The amount of handling required for this technique makes it unsuitable for repeated use in critically sick neonates.

4.2(d) Positron emission tomography

Positron emission tomography (PET) provides both anatomical and physiological information. Radio-active isotopes such as oxygen-^{15}, nitrogen-^{13}, carbon-^{11} and fluorine-^{18} which emit positive electrons (positrons) are used either directly in elemental form (for example gaseous oxygen) or to label compounds (for example water) to be used as tracers. The positrons interract with electrons after travelling a few millimetres to produce gamma rays by annihilation of the two particles which can be detected externally by a circular array. The interractlon sites can be precisely defined by the detection apparatus, enabling an image to be constructed. The isotopes used have relatively short half-lives (^{15}oxygen: 2 minutes; ^{13}nitrogen: 10 minutes; ^{11}carbon: 20 minutes; ^{18}fluorine: 100 minutes) which firstly reduces the radiation exposure time and secondly allows dynamic and serial studies to be performed.

Radio-labelled water ($H_2{}^{15}O$) is commonly used, since for a short period of observation it may be considered as an inert, freely diffusible tracer. For the first 40 seconds after injection, the local brain concentration of the tracer will depend on the local perfusion rate. The detected emissions are integrated and combined with frequent arterial sampling (every 5 seconds) to provide an estimation of perfusion.

Volpe et al (1983) used PET to assess regional CBF in neonates with parenchymal injury and to investigate the nature of such injury (whether ischaemic or harmorrhagic).

Other studies have used the technique to study cerebral glucose metabolism (Doyle et al 1983) and to observe CBF patterns following perinatal asphyxia (Volpe et al 1985) and during seizures (Perlman et al 1985a). Estimations of CBF by this method were found to correlate with Doppler estimations of blood flow velocity (Perlman et al 1985b).

As with the ^{133}Xenon technique, the blood-brain partition coefficient is required for the calculation of CBF. Underestimation of flow will arise both from local perfusion heterogeneity and if the flow is high, the latter resulting from limitations of diffusion (depending on the tracer used). Other potential sources of error include the accuracy of the arterial-to-brain delay. Apart from the concerns of using radio-active tracers (requiring cyclotron facilities for their production), the equipment is not portable and therefore does not lend itself to bedside use.

4.2(e) Near Infrared Spectroscopy

This is a relatively new technique, described by Jobsis (1977) and first performed on newborn infants by Brazy et al (1985). It may be used to measure a range of indices of brain oxygenation and haemodynamics and depends on the relative transparency of the neonate's head to near infrared light (wavelength 700-1000 nm) compared to visible light.

Near infrared light at the requisite wavelength is transmitted into the parietal region through a flexible fibreoptic bundle (optode). The transmitted light is attenuated by scattering and absorption in the tissues and the light emerging from the contralateral parietal region is collected by an identical fibreoptic bundle and conveyed to a sensitive photomultiplier tube. Attenuation resulting from scattering may be assumed to be constant, whereas changes in absorbed light depend on changes in the chromophore concentrations (haemoglobin and cytochrome aa_3) and the proportion of their oxygenated

and deoxygenated forms. In vitro studies have established algorithms relating (1) changes in light absorption (resulting from induced changes in chromophore concentration) to changes in blood volume (Jobsis 1977, Wray et al 1988) and (2) correcting for changes in optical path length resulting from scattering of light (Wyatt et al 1986, Wray et al 1988, Delpy et al 1988). To estimate CBF with this technique, the Fick principle is used:

$$Q = F \times {}_0\int^t (a-v)dt \qquad [2]$$

where Q is the amount of tracer in the tissue, F is the flow, and a and v are the arterial and venous concentrations of the tracer respectively. When the time t is less than the transit time through the organ, the tracer will not have reached the venous side. The flow can then be measured as the ratio between the amount of tracer accumulated in the brain and the amount of tracer introduced during the period (O-t).

The near infrared technique uses cerebral oxyhaemoglobin as the tracer and current devices measure both oxygenated and deoxygenated haemoglobin concentrations (HbO_2 and HB respectively), in addition to changes in total cerebral haemoglobin concentration. The inspired oxygen concentration is suddenly increased and the resulting increase in cerebral oxyhaemoglobin represents the accumulation of tracer. The product of the integral of change in arterial blood oxygen saturation (SaO_2; monitored by pulse oximetry) with respect to time and the arterial haemoglobin concentration (aHb) is the arterial tracer concentration and therefore:

$$CBF = k.\frac{\partial HbO_2 - HB}{aHb.\ {}_0\int^t (SaO_2)dt} \qquad [3]$$

where k is a constant.

This technique may be performed at the bedside and has been shown to produce estimates of CBF comparable to those obtained by other methods (Edwards et al 1988). Skov et al (1991) however found that the near infrared technique tended to underestimate CBF at higher flow rates compared to an intravenous ^{133}Xenon technique.

There are several important assumptions in the methodology of this technique and several criteria need to be satisfied for estimations of flow to be valid:

(1) The optical path length (see above) is a complex function of the geometrical distance between the two optodes, the amount of scattering elements (in turn dependent on gestational age, cell concentration, myelination and bone mineralisation) and the concentration of chromophores.

(2) The major problem with using an arterial tracer is that the transit time is very short (approximately 6 seconds; Skov et al 1991) and therefore the resolution of the near infrared and pulse oximetry equipment must be very good. In addition, the integration period t (7-8 seconds; Skov et al 1991) must be less than the minimum cerebral transit time.

(3) Before attempting estimations of CBF, cerebral oxyhaemoglobin and deoxyhaemoglobin concentrations and arterial oxygen saturations need to be stable for a period greater than the maximum cerebral transit time. In addition cerebral blood volume and oxygen extraction must remain constant during each measurement.

(4) The effects of changes in PaO_2 on CBF have already been discussed (see 3.4c) and

clearly the rise in PaO_2 induced by the increase in inspired oxygen concentration may influence the value of CBF obtained. In addition there may be certain situations where it is difficult to increase in SaO_2 (for example in the presence of severe lung disease, persistent fetal circulation, congenital cyanotic heart disease or indeed normal lung function), rendering the technique unable to be used.

4.2(f) Electrical Impedance

Electrical impedance is the resistance of a material to the flow of an alternating current. Transcephalic impedance is a method of estimating changes in volumes within the head of conductive elements such as blood and CSF. The change in impedance may thus be used as an index of CBF and has been used in adults (Auinger et al 1953), term (Reigel et al 1977) and preterm infants (Weindling et al 1983). Biological tissues present an impedance to the passage of an electrical current, which may be expressed by the equation:

$$Z = \frac{p.l^2}{V} \qquad [4]$$

where Z is the impedance, p is the resistivity, l is the length and V is the volume of the tissue studied. Therefore changes in cerebral blood volume which occur in each cardiac cycle will result in cardiac-synchronous changes in baseline cerebral electrical impedance. This change in impedance will be influenced by several factors including:

(1) Concurrent changes in blood resistivity which varies during the cardiac cycle, with changes in haematocrit and with red cell orientation secondary to changes in flow rate.

(2) Changes in intracranial blood volume, which also cause head expansion, CSF re-distribution and altered brain resistivity.

(3) Extracranial circulation.

To measure cerebral electrical impedance, two electrodes are attached to the scalp diametrically apart along the occipito-frontal circumference. A very small (2 mA) high frequency (100 kHz) alternating current is then passed through these "current-drive" electrodes. Further voltage-sensing electrodes are applied at various points along the head circumference to sample the electrical field set up by the drive electrodes.

Weindling et al (1983) monitored changes in CBF over both short and long periods (up to 48 hours) with this technique. They used the product of the change in impedance (ΔZ) and the heart rate (which has the dimensions of flow since ΔZ is proportional to blood volume) as an index of CBF in the short term. This was subsequently demonstrated to correlate with CBF determinations using venous occlusion plethysmography (Costeloe et al 1984). For longer term studies the variability of ΔZ was used to assess control of CBF.

In addition to the factors affecting impedance given above, other potential sources of error are changes in impedance at the skin-electrode interface, movement and electrical noise artefact and changes in electrode separation as the head shape varies with each cardiac cycle.

4.2(a) Doppler Ultrasound Velocimetry

The first report of the use of Doppler in the assessment of cerebral blood flow in neonates was by Bada et al (1979). Unlike the methods described above (excluding electrical impedance) which estimate volumetric CBF (as ml blood.$100g^{-1}$ tissue), Doppler blood flow techniques measure changes in velocity of red blood cells. Under certain conditions this may be related to volumetric blood flow (see below).

The Doppler principle essentially states that the frequency of transmitted waves from a source (S) measured at a point (P) will be higher than the transmitted frequency if (P) is moving towards (S) and lower than the transmitted frequency if (P) is moving away from (S) (figure 4.1). This principle was first described by Christian Doppler (1843) and applied to astronomy, but an everyday example of the Doppler effect is the change in pitch of a siren that is heard as an ambulance approaches and passes an observer. Using ultrasound waves (frequency >20kHz) generated by a piezoelectric crystal, the Doppler principle may be used to calculate blood flow velocity. The microscopic structure of blood (a suspension of cells and other particles in plasma) scatters ultrasound, enabling Doppler shift measurements to be made.

In medical applications the Doppler effect is modified slightly since the source and "observer" (the Doppler transducers) are at rest with respect to each other, and such devices work by detecting the change in frequency of a beam of ultrasound (usually in the frequency range 1-10 MHz) that is reflected or scattered from structures moving with respect to the transducer producing the beam. Thus for example the velocity of red blood cells in an insonated vessel may be expressed by the equation:

$$V = \frac{\Delta F \, . \, c}{2f \cos \emptyset} \qquad [5]$$

where f is the transmitter frequency, c is the velocity of sound in tissue, V is the velocity, ΔF is the Doppler shift frequency and $\emptyset$ is the beam-vessel angle (figure 4.2). If $\emptyset$ and f are constant the mean velocity may be said to be proportional to the mean frequency shift. It is important to minimise calculation errors related to the angle of insonation, and this

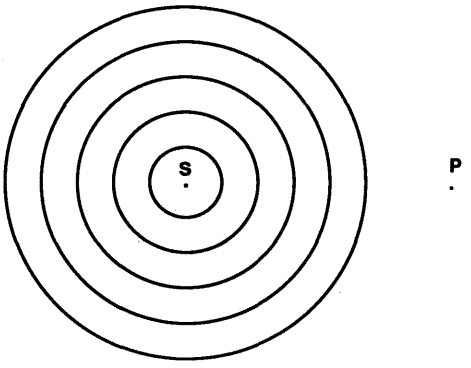

Figure 4.1a

Source of sound (S) stationary, thus wavelength of sound observed at point P remains constant.

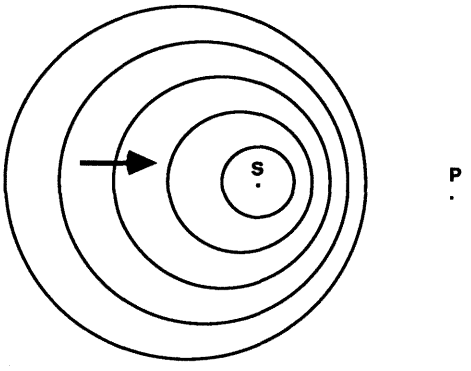

Figure 4.1b

Source (S) moving towards point P, thus wavelength of sound observed at point P appears to decrease, thus frequency increases - the Doppler shift.

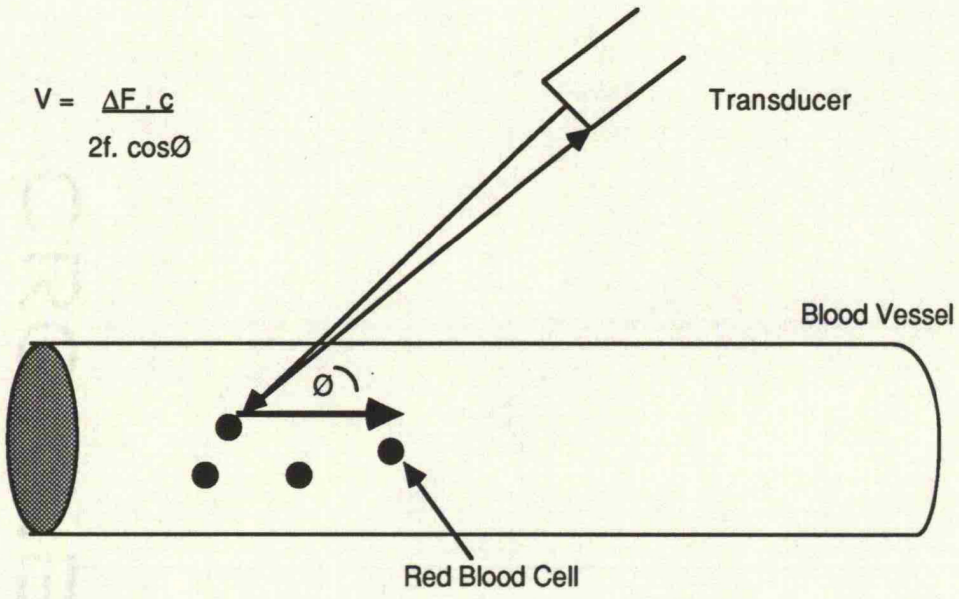

Figure 4.2

Calculation of blood flow velocity using Doppler shift.

is best achieved by keeping this angle to <10°. Conveniently, because of the range of transducer frequencies used and the range of ultrasound velocities in the body (0-4 $m.s^{-1}$), ∂f tends to lie in the audio-frequency range (0-20 kHz) and this allows an operator to monitor the Doppler signal simply by listening to it and adjust the transducer position to obtain the optimal signal.

Since red blood cells are smaller than the wavelength of the ultrasound, the echoes that they produce result from Raylelgh-Tindall scattering. In this process the cells absorb energy causing them to vibrate, subsequently emitting energy in a different direction as they return to their undisturbed state. The size of this echo is small compared to that produced by specular reflection from solid tissue interfaces, leading to blood-filled structures appearing echo-free. The shape of the red cells appears unimportant and in addition the intensity of the scattered ultrasound varies as the fourth power of the frequency. This has the practical implication that the performance of a Doppler system falls off with frequency less rapidly than that of a pulse-echo system, because the increase in scattered power with frequency partially offsets the increased attenuation of ultrasound by the intervening tissue.

The use of Doppler ultrasound has been validated both in vitro and in animal models in terms of its assessment of actual CBF. Animal studies of flow velocity showed good correlation with total brain blood flow using labelled microspheres (Hansen et al 1983, Batton et al 1983). Changes in CBF detected using Doppler correlated well with a radio-labelled Xenon technique in neonates (Greisen et al 1984) and adults (Bishop et al 1986). Using an in vitro model that mimiced the neonatal cerebral circulation, Lundell et al (1984) showed that the temporal mean of the space averaged velocity curve correlated closely with true flow. To calculate true cerebral blood flow using Doppler would need the cross-sectional area of the vessel being insonated. A change in diameter of 0.1 mm in a

vessel measuring 1 mm would result in a 20% change in cross-sectional area and in calculated flow, which is beyond the resolution of current imaging equipment.

A major assumption when using Doppler ultrasound is that the diameter of the vessel being studied remains constant. If this is the case, changes in flow velocity may be said to indicate changes in blood flow. Clearly for this assumption to be valid the factor resulting in a change in CBFV must exert its effects preferentially on small rather than major cerebral arteries (the latter being from where CBFV estimations are recorded). Such an effect occurs with changes in $PaCO_2$ (see 3.4e) and therefore the use of Doppler to estimate changes in blood flow would seem reasonable under these conditions. Other assumptions relate to the flow velocity profile across the vessel being insonated (see 5.3f[i]).

4.3 Summary

The characteristics of the techniques described above are summarised in table 4.1. Other methods for assessment of CBF include the use of radio-labelled erythrocytes (Arnot et al 1970) and thermal clearance. The latter method uses small variations in ear or fontanelle temperature as a qualitative measure of blood flow (Cross et al 1975a, 1975b). Neither method meets the criteria listed in 4.1 and have not gained widespread acceptance. Doppler ultrasound does meet these criteria with respect to the questions being addressed and was thus felt to provide the most suitable method of assessing changes in CBF in the population to be studied. The Doppler techniques to be used are discussed further in the following chapter.

Method	Variable Determined	Main Problems	Time Scale of Measurement
Kety-Schmidt/N_2O	Mean CBF	Requires arterial catheter. Arterial & venous sampling	20 minutes
^{133}Xenon Clearance	Mean CBF White/grey matter & scalp components	Requires injection of Radioactive tracer	30 minutes
Jugular Venous Occlusion Plethysmography	Mean jugular venous blood flow - hence derivation of total cranial blood flow	Repeated handling Raised ICP	10 seconds
Positron Emission Tomography	Mean and regional CBF	Repeated blood sampling Radioactive tracer	40 seconds
Near Infrared Spectroscopy	Mean CBF	Requires change in oxygen saturation Assumes constant cerebral blood volume & oxygen uptake	30 seconds
Electrical Impedance Plethysmography	Multifactorial, but primarily blood volume	High frequency current leak	Continuous
Doppler Ultrasonography	Cerebral blood flow velocity & ? cerebrovascular resistance	Ultrasound power	Intermittent or continuous

Table 4.1

Methods of assessment of neonatal cerebral blood flow.

Chapter 5

Doppler Assessment of Cerebral Blood Flow

5.1 Introduction.

5.2 Doppler assessment of blood flow.

- (a) Systems.
- (b) Recording and reproduction of signals.
- (c) Doppler power spectra.
- (d) Signal processing.
- (e) Blood velocity measurements.
- (f) Assumptions and problems with Doppler velocimetry.
  - (i) Arterial velocity profile.
  - (ii) Vessel calibre.
  - (iii) Safety of ultrasound.

5.3 Doppler assessment of neonatal CBFV.

- (a) Duplex systems.
  - (i) Arterial visualisation and insonation.
  - (ii) Reproducibility.
- (b) On-line system.
  - (i) Method.
  - (ii) Results.

5.1 Introduction

Having decided on Doppler ultrasound as the method by which to assess changes in blood flow (using blood flow velocity as an index of flow), the next question to address was the type of system to use. In addition, calculation of blood flow velocity, other related

indices and the problems and assumptions relating to this technique are considered.

5.2 Doppler Assessment of Blood Flow

(a) Systems

Doppler systems may be broadly divided into continuous wave (CW) and pulsed wave (PW). CW systems transmit and receive Doppler signals continuously and therefore have no range resolution, although signals from a larger distance from the transducer are more attenuated than those from nearer. In addition, they require two crystals, one to transmit and one to receive (generally housed in the same probe). Reflected ultrasound energy is reconverted to electrical energy by the receiving crystal. This is then amplified and mixed with a reference signal from a master oscillator. The process of mixing produces both the sum of the transmitted and received frequencies, and the required difference frequency or Doppler shift frequency. High frequency noise is then removed and a low pass filter removes low frequency signals due to other moving structures in the path of the ultrasound beam such as vessel walls. This leaves only the Doppler difference frequency which may then be amplified and used to drive a loudspeaker. The process of obtaining the Doppler audio signal from the Doppler shifted ultrasound signal is termed demodulation.

PW systems transmit short bursts of ultrasound at short intervals and receive only for a short period of time following a set delay, the length of the delay determining the range from which signals are gathered. The time that the transducer is receiving (and to some extent the receiver bandwidth) taken together with the length of the transmitted pulse determine the length of the sample volume and hence the proportion of the vessel width interrogated.

A major drawback of PW systems is that they are only be able to detect velocities

unambiguously up to a finite maximum related to the depth of examination. The Doppler shift signal itself is synthesised from a large number of discrete samples, one of which is made each time an ultrasound pulse is received by the transducer. The signal can theoretically be reconstructed from samples as long as the frequency of the signal is no more than half the sampling rate. This is known as the Nyquist limit and as long as the samples are taken rapidly compared to the rate of variation of the Doppler shift signal itself there is no problem. For example, a Doppler shift signal of 1 kHz can be represented by 5000 samples per second using a 5 kHz pulse repetition frequency (PRF).

However, the PRF is limited by the depth of the sample, since no transmission can occur before the preceding pulse is received. If the Doppler shift frequency of moving blood is greater than the Nyquist limit for that depth an ambiguous shift frequency will result. This effect is known as aliasing. An example of aliasing is the apparent backwards motion of the wheels of a cart seen on the television when the frame rate is inadequate to correctly reproduce the speed and direction of motion.

Aliasing can only be overcome by increasing the PRF, but this may lead to range ambiguity if there is more than one pulse with a significant size propagating in the tissue at the same time. This is a particular problem in cardiology, where there is a conflict of requiring a high PRF to measure the Doppler shift resulting from high velocity jets, and requiring a low PRF because of the relatively large distance from which measurements must be made.

Duplex scanners combine Doppler systems with pulse-echo B-scanners. The B-scan image is used to guide the Doppler beam and to place the sample volume at a known anatomical site. In addition, the angle Ø which the ultrasound beam makes with the direction of blood flow can be determined.

5.2(b) Recording and Reproduction of Signals.

Recording Doppler signals onto audiotape allows analysis to be performed at a later time. Digital audiotape has better specifications than analogue audiotape in terms of:

(1) Frequency response. This determines the range of Doppler frequencies that may be handled by the system.

(2) Signal to noise ratio. Intrinsic tape noise and that generated by the record/playback amplifier.

(3) Harmonic distortion. A measure of the degradation undergone by a signal recorded and played back through an audio cassette recorder; the distortion introduces additional frequency components known as harmonics.

(4) Input signal range. This specifies the input range within which the input should fall if it is not to be distorted.

(5) Wow and flutter. This arises due to variation in the rate at which the tape passes the record/play head.

(6) Crosstalk. This is a measure of the degree of unwanted signal transfer between channels in stereo or multichannel equipment.

5.2(c) Doppler Power Spectra

In practical (as opposed to theoretical) Doppler applications there are a large number of reflectors (red blood cells) moving with a range of velocities, and therefore the Doppler shift signal does not consist of a single frequency as suggested by the equation in 4.2(g), but of a wide band signal constantly varying with time. In the case of blood flow, the frequency spectrum would ideally correspond in shape to a velocity histogram of the blood cells within the sample volume. Factors which may influence the shape of this spectrum include:

(1) Aliasing. See 5.2(a).

(2) Filtering. Filters which remove low frequency components such as vessel wall motion

(see 5.2[a]) will also remove signals from slowly moving blood. This is of importance where normal velocities are low, for example in the neonate.

(3) Non-uniform insonation. If the sample volume is smaller than the vessel's diameter not all the frequencies across the vessel's width will contribute equally to the Doppler signal.

(4) Attenuation. Differences in attenuation of ultrasound occur depending on the relative amounts of blood and soft tissue the beam has to traverse. This effect is greater at higher frequencies and at greater angles of insonation.

(5) Intrinsic spectral broadening. Since the ultrasound beam has a finite width, the echoes arising from objects entering and leaving the beam rise and then fade. This is equivalent to the introduction of additional frequencies above and below the main Doppler frequency shift causing transit time broadening of the spectrum. Since most vessels contain blood moving at a range of velocities, the effect of this is to smear the Doppler shift power spectrum in relation to the velocity profile, parabolic flow being affected more than "plug" flow.

5.2(d) Signal Processing

The variation in the shape of the Doppler power spectrum as a function of time is usually presented in the form of a sonogram. Time is displayed along the x-axis, the Doppler shift frequency along the y-axis and the power (corresponding to a particular velocity and time) as the intensity of the resulting display.

Because of the complex nature of the Doppler power spectrum the best way to process the signal is to perform real time spectral analysis so that the evolution of the spectrum (which under ideal conditions has a similar shape to the velocity distribution of blood within the sample volume; see 5.2[c]) may be followed.

Analysis is implemented by the use of a digital alogarithm known as fast Fourier transform. Short periods of the signal (1-10 msec.) are digitised and analysed for their frequency components, producing a series of spectra in real time which represent the relative power of each frequency component constituting the Doppler signal. Spectral analysis provides only an estimate of the true power spectrum of the Doppler signal and is itself responsible for certain artefacts, for example related to the length of the segment analysed and the frequency at which analysis is performed.

5.2(e) Blood Velocity Measurements

Velocity may be calculated either from the mean frequency or the maximum frequency envelope of the sonogram. The method used in the following work is the maximum frequency follower, since the haemodynamic conditions that prevail in the neonatal brain (predominantly unidirectional, established laminar flow) are particularly suited to the application of this method (see below). Assumptions relating to the velocity profile in arteries are discussed further in 5.2f(i). The major advantages are that it is resistant to noise and to measures designed to reduce noise such as high pass filters (Evans et al 1989). In addition its output is fairly independent of the way in which the ultrasound beam samples the blood vessel. The output (a maximum frequency "envelope") is superimposed on the sonogram display to ensure that the desired part of the spectrum is being followed.

The relation between the instantaneous mean and maximum velocity in an artery depends entirely on the shape of the velocity profile. Where the flow profile resembles a plug, the mean and maximum velocities are equal, whilst if the flow profile is parabolic the maximum is exactly twice the mean (see below and 5.2f[i]). In pulsatile flow the velocity profiles may change quite dramatically during the cardiac cycle and thus the ratio of maximum to mean frequency in the Doppler signal will also vary widely.

In vessels supplying low-impedance beds, the maximum velocity in the vessel is in its centre throughout the cardiac cycle. Thus the ratio of the time-averaged Doppler frequency to the time-averaged mean Doppler frequency is the same as the ratio of the maximum velocity to the mean velocity in the time-averaged mean component of the velocity profile (Evans 1985). Thus if the shape of the mean velocity profile is known then the time-averaged mean velocity can be calculated from the time-averaged maximum velocity. If the mean velocity profile is parabolic, the time-averaged maximum velocity will be twice the time-averaged mean.

5.2(f) Assumptions and Problems with Doppler Velocimetry

(i) Arterial Velocity Profile

Arterial blood flow patterns are complex but useful approximations can be made using fairly simple models. The flow in the normal circulation is for the most part both laminar and pulsatile and may be considered as the sum of a steady flow component and a series of oscillatory components. In addition, the maximum frequency method (see 5.2[e]) assumes that the arterial system may be treated as a linear system with respect to pressure gradient and flow. Experimental results (Milnor 1982) suggest that despite the non-uniform nature of arterial diameter (both along its length and during the cardiac cycle at any one point) the arterial system can be treated as linear in terms of impedance. Thus the velocity profile will be parabolic (Caro et al 1978) and the time-averaged centre stream velocity will be twice that of the spatial average time-averaged velocity (see 5.2[e]).

5.2f(ii) Vessel Calibre

This has previously been discussed in section 4.2(g).

5.2f(iii) Safety of Ultrasound

Since ultrasound is a form of radiant energy, there have been some concerns expressed about its potential harmful effects on tissue (Bergman 1983). Ultrasound causes particles of the insonated medium to vibrate about an equilibrium position, thus propagating the pressure waves at a speed dependent on the properties of the medium. The accoustic intensity of the sound wave is defined as the rate of energy flow through unit area and is dependent on the amplitude of particle displacement, velocity, acceleration and frequency of the wave. Real-time scanning involves the use of pulse-echo imaging, in which the particles are exposed to the ultrasound field for extremely short periods at regular intervals (for example 1 μsec pulse at 1 msec intervals). Intensity of the pulse can be measured (temporal peak) or averaged over one full cycle (temporal average), the averaged values usually being about 0.1% of the peak. This measurement may be made at the position of maximum energy flow (spatial peak) or over the whole specimen (spatial average), the averaged values being 1/2-1/6 of the peak.

The adverse effects of ultrasound may be divided into thermal, mechanical and cavitational. The absorption of ultrasound by tissue produces heat, which may be dissipated by conduction through the tissue and by convection, via the tissue's blood flow. Ultrasound has been implicated in the twisting of cell membranes and rotation of intracellular bodies in the same way that the mechanical effects of audible sound cause vibration of the tympanic membrane.

Cavitation refers to the growth and subsequent behaviour of gas bubbles in insonated tissue. Transient cavities from high accoustic intensities may collapse rapidly, with the dissipation of much kinetic energy locally, leading to a rise in pressure and temperature. Stable cavities, which may be produced by frequencies lower than used in the clinical setting, act as oscillating bubbles, leading to vibration of cell surfaces or to

the generation of eddying movements in adjacent fluids.

Whilst it has been demonstrated that high-intensity ultrasound can cause tissue disruption, no consistent changes have yet been demonstrated following exposure to ultrasound for short periods at the intensities used in imaging. An extremely comprehensive review of the reports of deleterious effects following in vitro and in vivo exposure to ultrasound was made by Stewart et al (1985). The authors' main comments were that there were many small independent reports and that reported findings of microstructural changes at the cellular level as well as developmental problems such as dyslexia deserved further attention.

With regard to the fetus, a 12-year follow up study of 425 children exposed to routine antenatal ultrasound showed no biologically significant differences to matched controls (Stark et al 1984). Their assessment included conductive and neural hearing tests, visual acuity and colour vision, cognitive function, behaviour and neurological examination. Similarly, Salvesen et al (1992) found no difference in school performance or in the incidence of dyslexia in a large cohort of children tested at between 8 and 9 years of age compared to controls whose mothers had not had antenatal ultrasonography. However, the discovery of the deleterious consequences of X-rays should make us wary of pronouncing any source of radiant energy "safe" at an early stage of its clinical use.

Since the factors relevant to biological effects in patients have not been identified for low-intensity ultrasound, it is not possible to calculate the dose to the patient as might be done for ionizing radiation. However, the exposure of the patient can be minimised, using the following guidelines:

(1) Using the lowest transmitted power to obtain a result. The recommended maximum level is currently 100 $mW.cm^{-2}$ (AIUM 1984).

(2) Minimising the duration of the examination.

(3) Using the lowest PRF of the pulsed Doppler unit that will allow the highest velocity to be measured.

(4) Using CW rather than PW Doppler if it will give a result.

(5) Not leaving the Doppler beam irradiating a particular region for longer than is necessary.

5.3 Doppler Assessment of Neonatal CBFV

(a) Duplex Systems

(i) Arterial Visualisation and Insonation

The anterior fontanelle provides a useful accoustic window through which to insonate cerebral blood vessels in the neonate and infant. Using this approach, one anterior cerebral artery (ACA) is visualised in the sagittal plane and the Doppler sample volume positioned midway between its origin from the anterior communicating artery and the inferior-most point of the corpus callosum (plate 5.1). An alternative approach is to visualise one middle cerebral artery (MCA) in coronal section by placing the transducer over the temporal bone just anterior to and at the level of the helix of the ear. The artery is seen in the fold of the temporal lobe and the sample volume is positioned just before the vessel curves into the Sylvian fissure (plate 5.2). Using both of these approaches, blood flow is towards the transducer and the angle of insonation may be kept $<10^{o}$ (see 4.2[g]).

5.3a(ii) Reproducibility

Aim: To assess the reproducibility of neonatal CBFV estimations over short time periods using standard Duplex apparatus.

For the purposes of examining the cerebrovascular response to a rise in $PaCO_2$, it was decided to use standard duplex Doppler equipment to assess changes in CBFV, since only two estimations would be needed for each study and this could be achieved with a

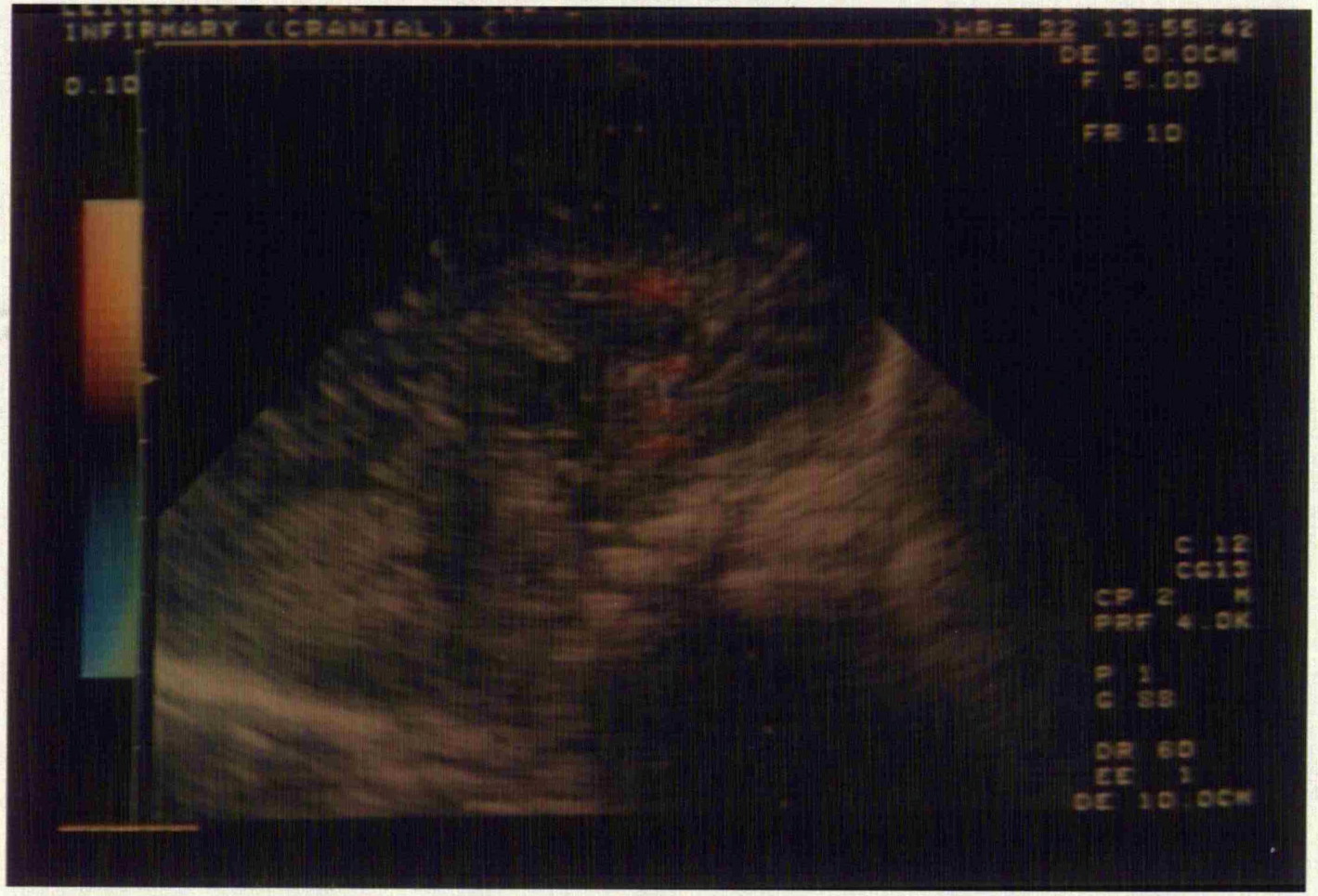

Plate 5.1

Anterior cerebral artery visualised through the anterior fontanelle using colour Doppler.

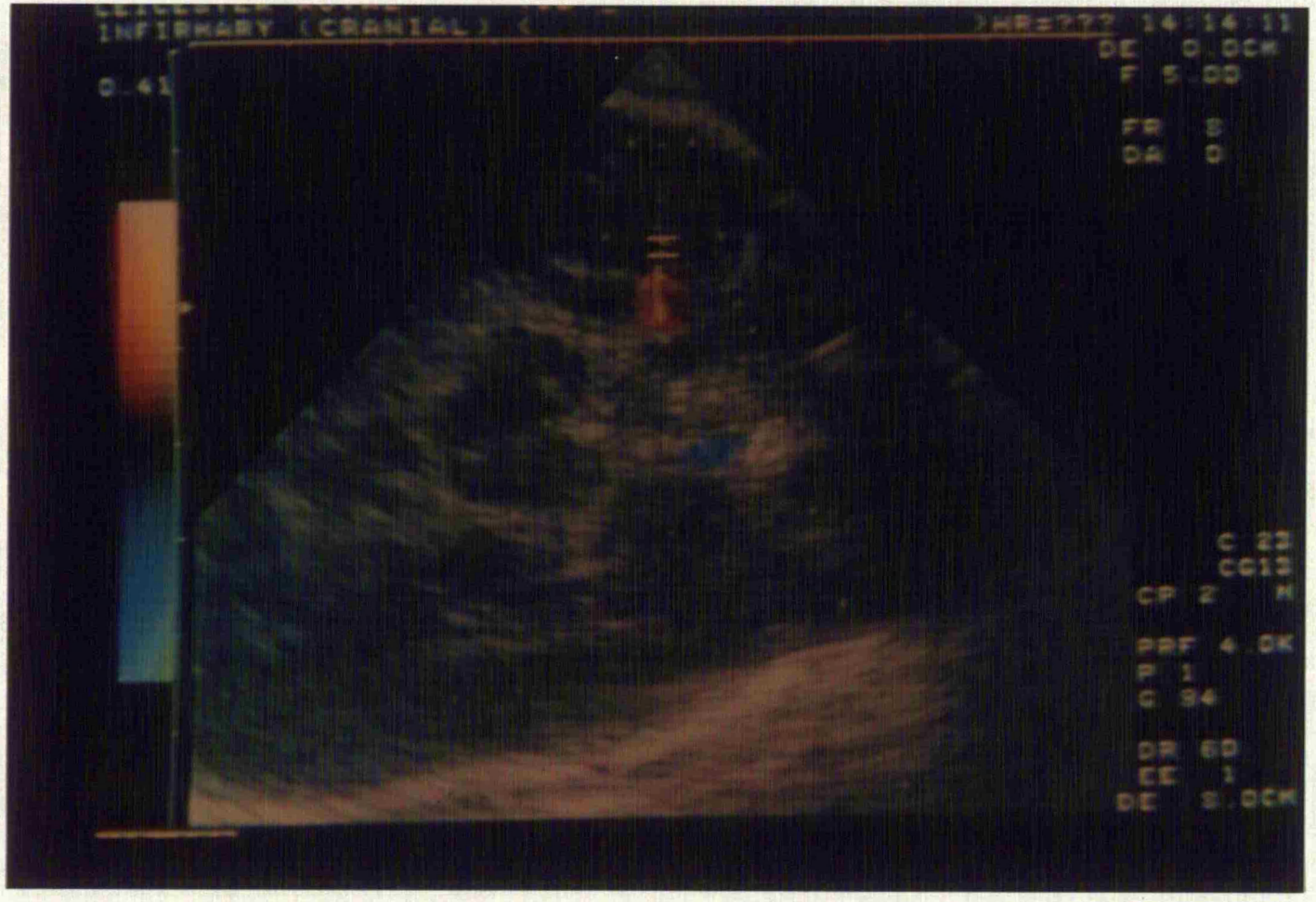

Plate 5.2

Middle cerebral artery visualised through the temporo-parietal region using colour Doppler.

minimal amount of handling. it was important to assess the degree of variability of CBFV estimations using such equipment in stable ventilated preterm infants, since merely placing the transducer on the infant's head might result in a change in CBFV. This might in turn influence any alteration in CBFV resulting from a rise in $PaCO_2$.

Sixteen infants were therefore studied on two occasions 10 minutes apart, the probe being removed between determinations. CBFV recordings were made using an ATL 600 duplex Doppler system with a 724A probe (pulse-echo 7.5 MHz, Doppler frequency 5 MHz). One ACA was visualised in the sagittal plane through the anterior fontanelle as described above (5.3a[i]). Care was taken to ensure that the angle of insonation was less than 10^{o} (see 4.2[g]).

For these recordings the Doppler sample volume was set to 3 mm and the high-pass wall filter at its lowest value (100 Hz; see 5.2[a] & [c]). The ultrasound intensity was kept as low as possible and never allowed to exceed 100 mW cm^{-2} SPTA (see 5.2f[iii]). Once the optimum Doppler signal had been obtained by listening to the audio signal and observing the sonogram in real time, 25 to 30 cardiac cycles were recorded onto digital audio tape for analysis (see 5.2[b]).

The Doppler tapes were replayed through a fast Fourier transform analyser (see 5.2[d]) and the maximum frequency envelope of 20 or more consecutive beats were extracted and calibrated in terms of velocity using the Doppler equation (5.2[a]). The mean velocity over the cardiac cycle was estimated by halving the mean value of the maximum velocity over the cycle (see 5.2[e] and 5.2f[i]). The minimum change in CBFV detectable with this method is 0.5 $cm.s^{-1}$.

infant details are shown in table 5.1. The two estimations of CBFV were examined

Gest.	Age (hrs)	CBFV Estimation (cm.s $^{-1}$) 1	2	Difference (1 - 2)	Mean (1&2)
25	143	5.0	6.0	-1.0	5.50
26	73	4.0	4.0	0.0	4.00
26	129	4.5	5.0	-0.5	4.75
27	61	4.0	3.0	1.0	3.50
27	125	7.5	8.0	-0.5	7.75
28	25	6.0	5.5	-0.5	5.75
28	110	3.5	3.5	0.0	3.50
29	2	3.5	4.0	-0.5	3.75
29	47	5.0	5.0	0.0	5.00
30	9	4.0	5.0	-1.0	4.50
30	92	5.0	5.0	0.0	5.00
31	15	4.5	4.0	0.5	4.75
31	63	7.0	6.0	1.0	6.50
32	77	8.5	8.5	0.0	8.50
33	50	9.5	10.0	-0.5	9.75
34	51	8.0	8.0	0.0	8.00

Table 5.1

Paired estimations of baseline CBFV in 16 infants to determine (a) reproducibility and (b) whether effects of handling on first occasion affected second estimation.

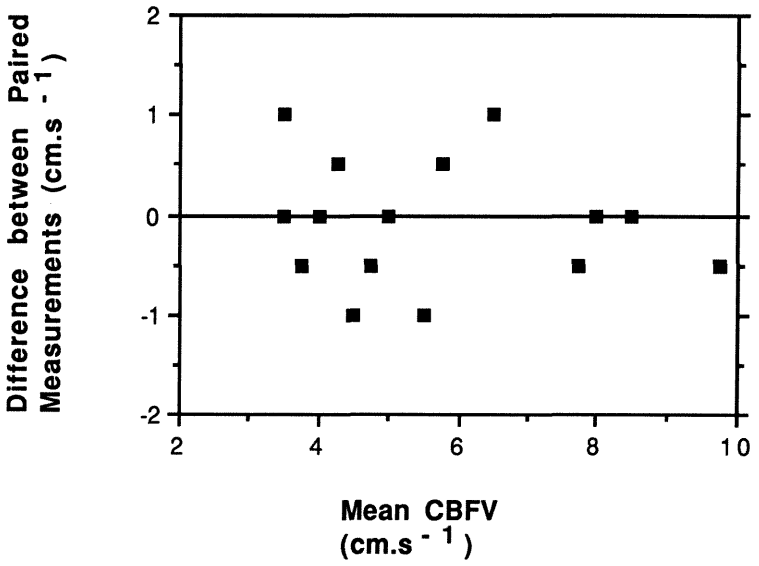

Figure 5.1

Difference between paired measurements of CBFV plotted against their mean.

using the method of Bland and Altman (1986), the difference between paired estimations being plotted against their mean (figure 5.1). This did not suggest any consistent effect of handling between the two estimations. The mean of the differences between paired estimations was -0.06 $cm.s^{-1}$ (SD 0.6 $cm.s^{-1}$).

5.3(b) On-Line System

Aim: To evaluate a purpose-built Doppler system for estimating changes in neonatal CBFV over prolonged periods.

Sick preterm infants tolerate repeated handling poorly. For studies requiring multiple CBFV estimations over a short period of time a system was assembled to enable the recording, analysis and display of both CBFV from the middle cerebral artery (MCA) and blood pressure data at pre-set or manually determined intervals using a small button transducer fixed to the infant's skin, thus (a) obviating the need for repeated handling and (b) allowing "normal" fluctuations in CBFV to be observed in more detail.

5.3b(i) Method

The system is shown schematicaliy in figure 5.2. The pressure front-end is attached to the infant's in-dwelling arterial catheter, allowing measurement of blood pressure (see 6.4c[1]). The Doppler unit consists of a Doptek 4 MHz PW unit with a small button transducer (diameter 11 mm, depth 7 mm), specifically designed and built for this purpose. The ultrasound intensity is below 50 mW cm^{-2} SPTA (see 5.2f[iii] and A.i.U.M. 1984).

The use of PW ultrasound has two main advantages over CW in this particular setting: firstly it requires only a single, fine coaxial cable between the Doppler unit and transducer, reducing cable drag on the transducer thus making fixation easier. Secondly, it allows the signals from the ipsilateral and contralateral middle cerebral arteries to be

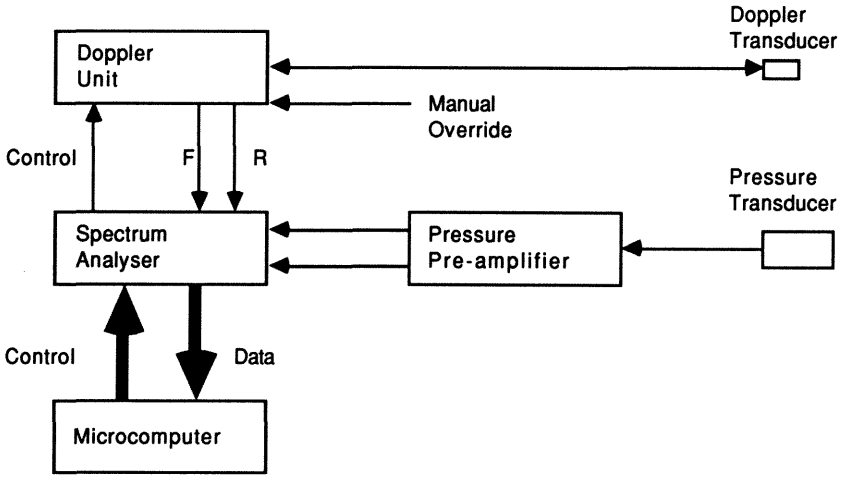

Figure 5.2

Schematic layout of on-line system. (F= forward, R= reverse channels)

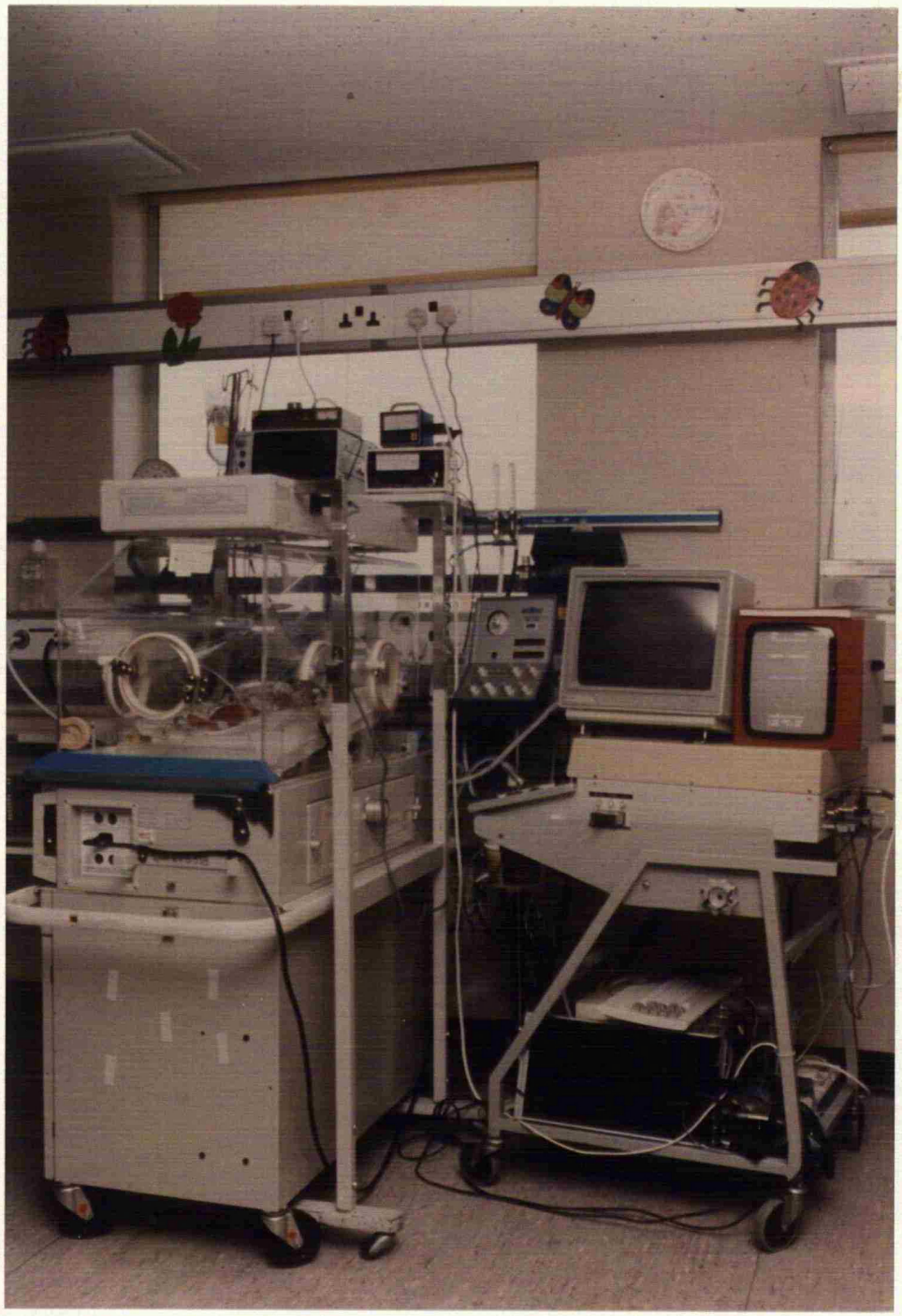

Plate 5.3

On-line system at cotside.

distinguished even when reverse blood flow in the vessel is present.

The remainder of the system comprises a spectrum analyser and microcomputer. The entire assembly occupies a small trolley which could be left at the cotside and did not interfere with routine nursing and medical care (plate 5.3). The small size of the transducer was found to be very acceptable to parents.

Positioning and fixation of the transducer is critical, since it has to be able to collect data for periods of several hours. The Doppler unit is activated and the transducer moved over the temporal bone until the optimal signal is obtained from the ipsilateral MCA. The position is marked, the skin cleaned of excess gel and the transducer then fixed in position using collodian. Following fixation, the sample volume depth and length could be adjusted to further optimise the signal. No local adverse effects were observed from fixation of the transducer.

Once set up, the software activates the Doppler unit at pre-set intervals. In addition there is a manual override facility, allowing the system to be activated to capture changes in CBFV and blood pressure associated with changes in the infant's clinical condition. Following activation, 12 seconds of blood pressure and spectrum analysed Doppler data are acquired by the microcomputer. The Doppler unit is then switched off. A maximum frequency envelope (see 5.2[e]) is derived from the Doppler data as described by Schlindwein et al (1988), and after the data are split into individual cardiac cycles, various parameters including mean velocity (and its coefficient of variation) and received Doppler power are calculated. Since accurate measurement of vessel diameter cannot be achieved, cerebrovascular resistance cannot be measured directly, but an index of resistance can be calculated by dividing mean blood pressure by mean blood flow velocity for each recording. Vascular resistance is defined as mean blood pressure divided by mean

blood flow, and therefore this index is the product of the peripheral resistance and the cross-sectional area of the vessel at the site of insonation, or resistance area product (RAP; Evans et al 1988). The results are written to disk and displayed graphically at the cotside.

The system was initially used on 33 infants being ventilated for IRDS (table 5.2). The gestational age (24-41 weeks) and weight range (750-3510g) of the group studied is representative of the population seen in the majority of neonatal intensive care units. The average length of study was 3.9 hours (range 1.5-9 hours) and in the majority of cases (29 out of 33 studies) it was decided to electively discontinue the study. In 4 infants, the infant's own movements or the nurses turning the baby caused significant degradation in signal quality to the extent that further recordings were not possible without reapplication of the transducer.

Studies were planned to commence immediately after nursing care had been given to minimise periods of handling. The study was discontinued if a change in position at the next care resulted in the infant's head lying on the Doppler transducer, which could potentially damage the infant's skin. The transducer could alternatively be re-applied to insonate the contralateral MCA.

The major problem encountered was maintaining transducer alignment and hence Doppler signal quality for prolonged periods. The system worked best in relatively inactive or therapeutically paralysed infants who were receiving minimal nursing and medical handling. This group of infants tends to be the most critically sick and therefore most at risk of developing neurological sequelae.

Study	Gestation	Weight (kg)	Sex	Duration (hrs)	Commant
1	30	1.26	M	3.25	Well infant, headbox oxygen, no apnoea
2	29	0.88	M	3.50	Stable infant on low ventilation
3	28	0.95	M	7.00	Severe RDS, paralysed
4	33	1.60	F	5.75	Moderate RDS, stable
5	32	1.62	M	8.00	RDS, previous pneumothorax
6	32	1.55	F	9.00	Stable RDS
7	31	1.20	F	5.00	Active infant, intermittent Doppler trace
8	26	0.99	M	5.50	Paralysed, severe RDS, poor Doppler last hour
9	34	2.48	M	3.00	Paralysed, severe RDS, no arterial line
10	32	1.67	M	4.33	Moderate RDS, unparalysed
11	34	2.06	F	4.75	Severe asphyxia
12	27	1.06	M	3.67	RDS, paralysed
13	41	3.51	M	4.00	Asphyxia, intermittent Doppler trace
14	27	1.10	M	1.50	RDS, paralysed, recording during rate changes
15	29	1.61	M	8.00	Well infant, good trace throughout
16	24	0.75	F	2.50	Extreme preterm, intermittent Doppler trace
17	30	1.20	M	2.50	RDS, good trace throughout
18	30	1.55	F	1.50	RDS, moderate ventilation, unparalysed
19	25	0.76	M	3.50	RDS, minimal ventilation, poor Doppler trace
20	25	0.72	F	4.00	Minimal ventilation, good trace
21	29	1.36	M	2.00	Moderate RDS, good trace
22	28	1.11	F	5.33	Non-ventilated, good trace
23	28	0.92	F	1.75	Non-ventilated, poor trace
24	31	1.45	M	3.33	Moderate RDS, paralysed, good trace
25	26	1.15	M	3.75	Moderate RDS, unparalysed, good trace
26	27	1.30	M	3.50	RDS, PDA, Indomethacin given during study
27	29	1.40	M	1.50	RDS, unparalysed, poor BP trace
28	27	0.92	M	3.00	Dead space in circuit
29	26	0.85	F	5.00	RDS, paralysed, probe re-sited
30	32	2.07	M	2.00	RDS, paralysed
31	32	1.79	M	3.75	Severe RDS, paralysed
32	30	0.72	M	2.00	Moderate RDS, unparalysed
33	31	1.60	M	3.00	RDS, paralysed

Table 5.2

Clinical details of infants studied using on-line Doppler system.

5.3b(ii) Results

A typical trace from an infant of 29 weeks' gestation being ventilated for respiratory distress syndrome is shown in figure 5.3. Several features on the traces are worthy of note. Inadequate flushing of the in-dwelling arterial line resulted in damping of the blood pressure trace (point a, upper trace). Any activity on the part of the infant or any handling such as turning the infant resulted in a change in CBFV, in this case an increase (point b, middle trace). This highlights the inadequacies of intermittent sampling of CBFV with conventional equipment.

The potent cerebrovascular effects of changes in $PaCO_2$ are demonstrated in figure 5.4. A reduction in the inspiratory pressure of an infant being ventilated for respiratory distress syndrome resulted in an immediate rise in CBFV (point c). Repeat arterial blood gas sampling (point d) confirmed the rapid rise in $PaCO_2$ and returning the ventilator pressure to its original setting restored the $PaCO_2$ level and CBFV to their previous levels. A similar effect was obtained by inserting a dead space into the ventilator circuit (point e) causing a rise in $PaCO_2$ and then removing it (point f).

Several drugs which may have profound effects on the circulation are used in neonatal intensive care. For example, indomethacin is used in the medical management of patent ductus arteriosus. Administration of indomethacin (figure 5.5, point g) results in a sustained fall in CBFV and a sustained rise in RAP, which presumably indicates vasoconstriction (Levene et al 1988). The rise in CBFV immediately prior to drug administration is due to handling of the infant.

With regard to cerebrovascular CO_2 reactivity, a major variable in the infants to be studied would be the ventilatory modalities used, and as mentioned in 3.6 these might

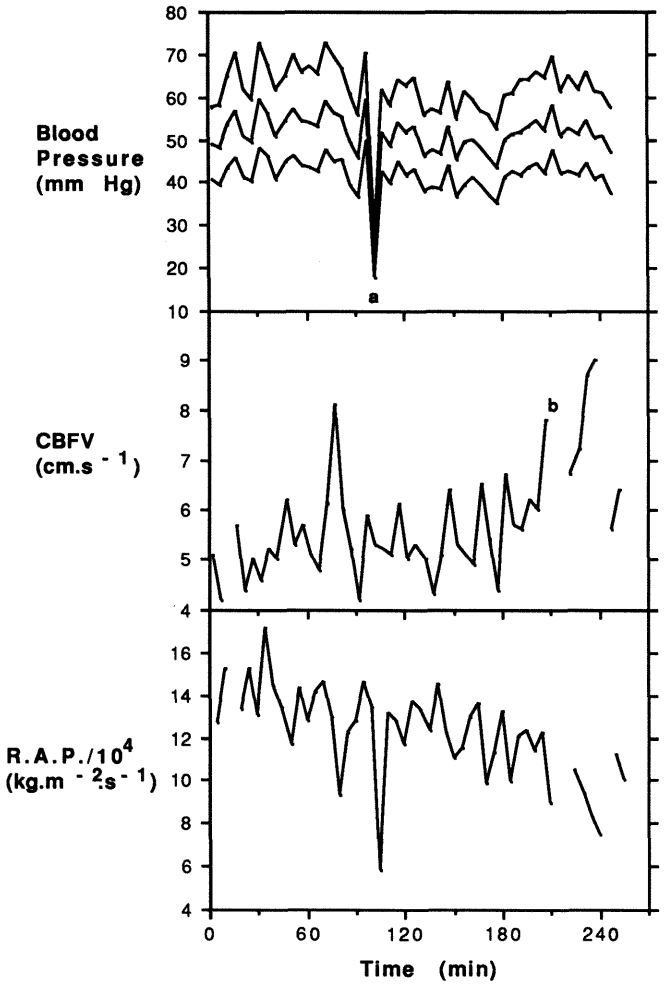

Figure 5.3

Normal fluctuations in CBFV. See text for details.

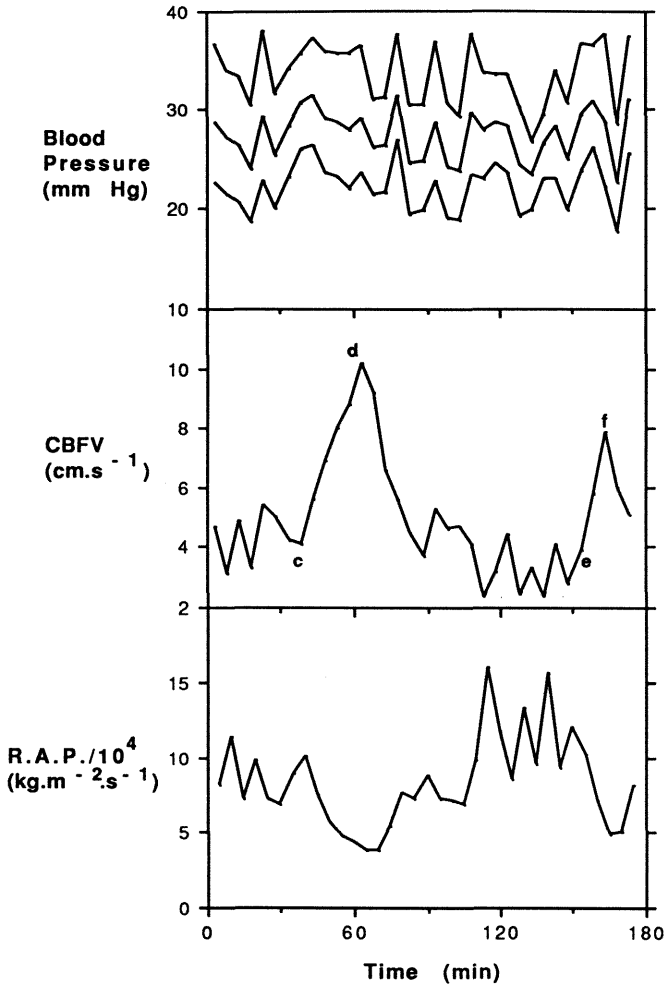

Figure 5.4

Effects of rises in $PaCO_2$. See text for details.

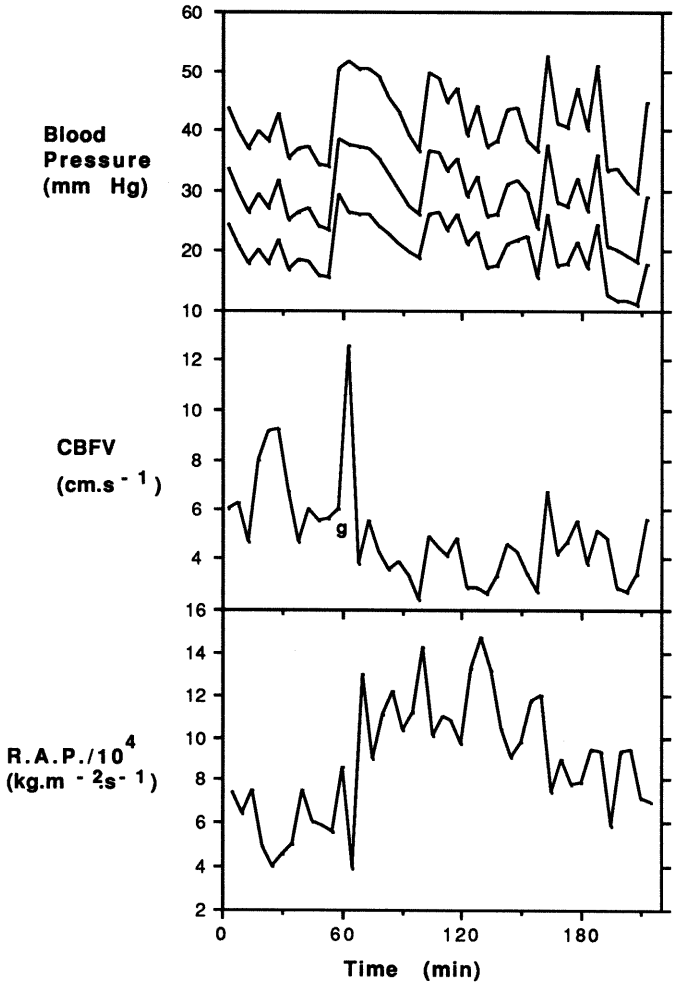

Figure 5.5

Effects of Indomethacin. See text for details.

potentially exert effects on circulatory parameters such as blood pressure and CBF. Previous work examining such effects are reviewed in the next chapter and the on-line system is utilised in a study to examine the circulatory effects of ventilator rate.

Chapter 6

Circulatory Effects of Ventilatory Parameters

6.1 Introduction

The widespread adoption and early use of ventilatory regimes as recommended by Reynolds (1971) and others was a major factor in the reduction of mortality from IRDS in preterm infants. As mentioned previously (3.5), the use of mechanical ventilation is associated with related problems, for example a not inconsiderable morbidity due to barotrauma. Clearly, acute events such as pneumothorax have the potential to seriously compromise the circulation, but in addition ventilatory parameters such as peak inspiratory pressure (PIP), positive end-expiratory pressure (PEEP) and ventilator

rate may also have adverse circulatory effects, as may the infant's interaction with the ventilator. Since it was intended to perform CO_2 "challenges" on infants whilst they remained ventilator dependent (chapter 7), each individual's ventilatory requirements might change between studies and in turn affect the circulatory response to the rise in $PaCO_2$. The potential circulatory effects of these factors therefore need to be considered, and a study examining the circulatory effects of ventilator rate will be presented.

6.2 Effects of Peak and Positive End-Expiratory Pressure

Cowan and Thoresen (1984, 1987) found that as PIP in ventilated infants was increased, so did the influence on both cerebral arterial and venous blood velocities, venous effects being seen first. The gestational age and size of the infants studied varied greatly and no compliance measurements were made, which is an important factor in determining whether changes in intrathoracic pressure due to ventilation are transmitted to mediastinal structures (see below). The order of effects reported (venous before arterial) may reflect the relative values of inspiratory, venous and arterial pressures, or be due to the course of vessels within the mediastinum relative to the lungs.

A rise in the amount of PEEP in adults leads to a rise in intrathoracic pressure. This may lead to a rise in CVP relative to atmospheric pressure, thus impeding venous return to the heart (Jardin 1981). Right-sided cardiac filling pressure will be reduced causing stroke volume to fall. Left-sided stroke volume will subsequently be reduced, resulting in a fall in ABP. This, combined with the rise in CVP may result in a fall in cerebral perfusion pressure (CPP), since the latter depends on the difference between arterial and central venous pressures. No compensation for the change in CPP occurred up to several hours after such an increase in PEEP (Qvist et al 1975). Another effect of the rise in CVP is a rise in intracranial pressure (Huseby et al 1978). The latter effect

appears to be independent of both arterial pressure and $PaCO_2$.

This series of events could be attenuated in anaesthetised animals by partial lung embolisation (Aidinis et al 1976, Huseby et al 1978) or by lung lavage with normal saline (Mirro et al 1987), both of which reduce lung compliance, or by transfusion (Qvist et al 1975). The role of reduced lung compliance in reducing these adverse effects of PEEP is important in the neonatal situation. Shortland et al (1989) showed no impairment of CBFV or blood pressure at three levels of PEEP commonly used in neonatal ventilation (2, 4 and 6 cm of water). Indeed, CBFV increased with increasing PEEP, although this was secondary to the accompanying rise in $PaCO_2$.

Although compliance was not measured in this study, it may be assumed that the infants studied had poorly compliant lungs. Hausdorf and Hellwege (1987) showed a reduction in systemic and pulmonary blood flow in preterm infants at PEEP settings of 8 cm of water but this was not associated with changes in heart rate or blood pressure in the short term. This study again did not measure lung compliance.

Most studies have implicated increased intrathoracic pressure and impaired venous return as the basis for adverse cardiovascular effects of PEEP (Pick et al 1982). The increase in lung volume results in an increase in pulmonary vascular resistance, leading to an increase in right ventricular afterload. In addition, the increase in pleural pressure transmits the PEEP onto the heart. The fall in right ventricular stroke volume results in a fall in left ventricular stroke volume on the basis of a Frank-Starling mechanism.

Another potential factor which might reduce cardiac output as a result of PEEP is the release of negative inotropic factors such as prostaglandins from the lungs. Patten et

al (1977) demonstrated a bilateral decrease in cardiac output in cross-circuiated dogs when one animal was given PEEP, and pre-treating with prostaglandin-synthetase inhibitors reduced the expected fall in blood pressure during ventilation (Said et al 1972). In addition reduction in cardiac output with increasing PEEP has been reported in thoracotomised dogs (Manny et al 1978), which clearly negates any transmission of pressure from the lungs on the heart and great vessels. Other mechanisms which have been suggested are impairment of cardiac function due to increasing right ventricular afterload distorting the intraventricular septum (Jardin et al 1981) and myocardial ischaemia resulting from impairment of coronary blood flow by PEEP (Pick et al 1982). The latter mechanisms have yet to be shown to be important clinically in humans.

6.3 Effects of Infant Respiratory Activity.

The infant's own respiratory pattern may affect cardiac output and hence CBF. Inspiration normally produces a fall in intrathoracic pressure which draws blood into the right side of the heart, thus increasing right-sided cardiac output. The drop in intrathoracic pressure also has the effect of causing pulmonary vasodilatation, reducing pulmonary venous return. Thus ieft-sided cardiac output and hence blood pressure fall. This effect results in the phenomenon of pulsus paradoxus. These variations are small In health, but may be exaggerated in the sick neonate.

Using intermittent positive pressure ventilation it would be expected that the rise in pleural pressure and lung volume during the inflation phase might reduce right atrial return and increase right ventricular afterload, as well as reducing aortic flow. Using a dog/normal lung model, Scharf et al (1980) demonstrated an inspiratory fall in pulmonary artery flow, with the nadir being at end-inspiration. This was followed by a reduction in pulmonary venous return to the heart and hence a fall in aortic flow over each respiratory cycle several heart beats after the fall in pulmonary flow. Thus the nadir of

aortic flow occurred at end-expiration.

However, the initial change in arterial pressure is an increase at the start of inspiration, a phenomenon which has been termed reversed pulsus paradoxus (Morgan et al 1966). In addition, the pulse pressure also increases, so this change cannot simply be due to transmission of intrathoracic pressure to the left ventricle. Jardin et al (1983) studied 13 ventilated adults (8 of whom had adult respiratory distress syndrome) and concluded that the increase in arterial blood pressure arose from enhanced pulmonary venous return during inflation, thus increasing left ventricular preload, with other factors such as reduced left ventricular afterload, enhanced left ventricular performance (secondary to compression) and alpha-adrenergic discharge occurring synchronously with lung inflation all being of relatively minor importance. The associated compromise of right-sided output will affect left-sided performance after a lag of 1-2 beats.

Rennie et al (1987) studied 20 ventilated infants with a birth weight of <2500g and measured the variability of CBFV on several occasions in the first 3 days of life. This variability was seen to fall over the first 48 hours and it was suggested that it reflected variability in CBF, since changes in cerebral artery calibre would not occur rapidly enough to affect beat-to-beat variability (Kontos et al 1978). Smaller fluctuations in variability were seen in those infants breathing synchronously with their ventiiator.

A similar fluctuating pattern of CBFV had been noted by Perlman et al (1983). This reflected blood pressure variability and could be reduced by paralysis with pancuronium (Perlman et al 1985c). Infants who demonstrated this increased variability had an increased incidence of IVH but the severity of the haemorrhage and subsequent clinical progress were not stated.

Rennie et al postulated that the fall in variability over time may be due either to relative vasodilatation of the cerebral vasculature in the first few hours of life (as proposed by Drayton & Skidmore 1987) resulting in less damping of blood pressure pulses reaching the cerebral circulation or to a lesser degree of blood pressure fluctuation after the first few hours. Changes in lung compliance as their respiratory disease evolved was again not measured in these infants.

6.4 Circulatory Effects of High Frequency Positive Pressure Ventilation (HFPPV)

Hypothesis: The use of HFPPV adversely affects blood pressure and hence cerebral blood flow, mediated via inadvertent PEEP.

(a) Introduction

Over recent years, the population of neonatal units has changed (Field et al 1985a) and the extremely immature infants now encountered on a regular basis are even more at risk from respiratory complications of IRDS. Additionally, neonatal ventilators are now more sophisticated and these factors have led to different patterns of ventilation being tried in attempts to minimise the complications of respiratory support.

The use of one such alternative, high frequency positive pressure ventilation (HFPPV) in neonates has been increasing, due to both a reported reduction in harmful interaction with the infant's own respiratory efforts (Pohlandt et al 1985) and an improvement in oxygenation in unparalysed infants (Field et al 1985b). Concerns about HFPPV have centred around the production of inadvertent PEEP (Simbruner 1986), resulting from insufficient time for the lungs to empty during the expiratory phase. This may lead to harmful secondary effects on both the lungs and the cardiovascular system. The former effect may impair blood gases and the latter may produce a number of secondary problems, for example decreased venous return, or restriction of left ventricular filling (see 6.2 & 6.3).

Several factors are likely to influence whether inadvertent PEEP occurs and whether its effects are transmitted to the cardiovascular system. Theoretically, it is more likely to occur in paralysed infants who cannot actively expire and if the degree of air leak around the endotracheal tube is relatively small. Mechanical transmission of inadvertent PEEP to the cardiovascular system will be affected by lung compliance (see 6.2), which will vary with the stage of IRDS. The aim of the following study was to examine the changes produced by HFPPV on arterial blood pressure and CBFV in a group of paralysed infants in the acute phase of IRDS and to determine whether such changes might be attributable to inadvertent PEEP .

6.4(b) Patients

The study group consisted of twenty infants, studied on one occasion each. Their birthweights ranged from 0.72-2.42 kg (median 1.48 kg) and their gestational ages from 25-34 weeks (median 30 weeks). The median age at the time of study was 54.5 hours. Median peak inspiratory pressure (PIP) at the time of the study was 24 cm of water and median inspired oxygen concentration was 0.73. Full details of the infants are given in table 6.1.

Infants were considered eligible for the study if they were being ventilated for IRDS and were paralysed with pancuronium to facilitate ventilation. The decision to use pancuronium was based on the inability to ventilate the infant satisfactorily at either slow or fast rates and was made independently by the clinicians responsible for the infant's care. All infants had an indwelling arterial catheter (either umbilical or radial) placed for clinical reasons and were intubated orally with shouldered endotracheal tubes. Infants were excluded if a pneumothorax was present, if there was pre-existing intraventricular haemorrhage or if the infant's condition was unstable.

Infant	Gestation (weeks)	Birthweight (kg)	Age at Study (hrs)	FIO_2	PIP (cm H_2O)	PEEP
1	29	0.90	124	0.86	22	2
2	30	1.50	77	0.75	28	2
3	32	2.00	66	0.60	20	2
4	32	2.07	66	0.80	23	3
5	31	1.99	73	0.70	26	4
6 *	30	1.70	14	1.00	32	4
7	30	1.28	81	0.98	31	3
8	29	1.36	43	0.78	25	2
9	32	2.07	20	0.58	20	2
10*	26	0.88	57	0.96	26	2
11	32	1.79	21	0.84	35	4
12	30	1.55	49	0.70	25	2
13	27	1.10	216	0.35	15	2
14	29	1.40	22	0.58	20	3
15*	25	0.75	16	1.00	20	2
16	31	1.45	38	0.58	20	4
17	27	1.06	144	0.65	20	3
18	30	0.72	86	0.50	20	3
19	31	1.60	23	0.46	28	2
20	34	2.42	52	1.00	32	3

Table 6.1

Details of infants at time of study. (*) denotes infants who died (all related to acute IRDS).

6.4(c) Measurements

The following parameters were recorded:

(i) Arterial Blood Pressure

Continuous intra-arterial monitoring of blood pressure was used in all infants studied and a permanent record of blood pressure made onto a chart recorder (Gould). The infant's in-dwelling arterial line (either umbilical or peripheral) was connected to a pressure transducer (Spectramed P23XL) by a length of non-compliant manometer tubing. The system is flushed with a heparinised solution at 1 $ml.hr^{-1}$, which is adequate to prevent line blockage. The main technical problems with this type of system relate to:

(1) Static pressure drop. There is a small but potentially significant resistive pressure drop between the pressure transducer and the blood vessel. This pressure drop depends on the type of catheter used, the viscosity of the infusing fluid and the rate of infusion. The error produced using 5Fr and 24Ga arterial catheters is <1mm Hg (Evans et al 1986).

(2) Frequency and phase responses. All blood pressure measurement systems that rely on hydraulic coupling to external transducers will produce some distortion of the waveform. The significance of this distortion will depend on both the shape and the frequency of the waveform, and on the information that is to be extracted from it. The catheter and filling fluids used in this system results in a degree of underdamping, which will over-estimate the pulse pressure, but frequency and phase responses are adequate (Evans DH et al 1986). Regular checks were made to ensure that the system was free of air bubbles and that there were no mechanical obstructions (for example kinking or compression of lines) which would affect the waveform. In all infants, mean arterial blood pressure (MABP) was recorded at each stage of the study.

6.4c(ii) Respiratory Data

Ventilator pressures were recorded directly from the endotracheal tube via a 19 guage needle connected to a pressure transducer (Elcomatic EM 751A). The frequency

response of this type of transducer (>10 Hz) is satisfactory for this type of measurement (Asher et al 1982).

Tidal volumes were recorded using a Gaeltec (8T-2) pneumotachograph in series with the endotracheal tube. The pneumotachograph is combined with a differential pressure transducer, which detects the pressure drop across a resistance within the pneumotachograph and this is proportional to flow. Tidal volume is obtained by electronic integration of the flow signal. Calibration of this system was performed by passing known volumes of air from a syringe through the pneumotachograph. All signals were recorded on a chart recorder for later analysis. The pneumotachograph was heated to prevent condensation on the internal gauze and the deadspace effect due to the internal volume of the pneumotachograph overcome by the use of a bias flow system. This was achieved by connecting a suction pump (Airshields Diapump) to the distal portion of the pneumotachograph via a 21 guage needle. The bias flow was measured (by rotameter) to bleed 2 litres per minute from the ventilator circuit through the pneumotachograph and did not affect performance.

6.4c(iii) Cerebral Blood Flow Velocity

In three of the infants CBFV recordings were made from one ACA using an ATL 600 duplex Doppler system and analysed as described in 5.3(a), the same precautions being observed with regard to angle of insonation of the vessel and adjustment to obtain the optimum signal. In addition the same general precautions pertaining to minimal handling were taken during each study. Firstiy, the infant's position was not aitered greatiy and particular attention was given to avoidance of neck flexion or extension, which could displace the endotracheal tube and thus change the efficacy of the ventilation. Excess pressure on the fontanelle when applying a hand-held transducer was avoided and at the end of the study all the ultrasound contact gel was wiped off the infant to minimise any

cooling effect. All equipment was cleaned with 70% isopropyl alcohol solution at the end of each study to reduce the possibility of cross-infection. The remaining 17 infants studied had CBFV measurements recorded from one MCA using the on-line system described in 5.3(b).

6.4(d) Study Procedure

Following attachment of the recording apparatus, a period of 15 minutes was allowed for any stabilisation of the infant's condition. All infants were then studied at three ventilatory rates: 30-40, 50-60 and 100/min, using a Sechrist ventilator (model IV-100B). PIP, PEEP and inspiratory : expiratory ratio were kept constant. The rate change sequence was initially an increase in all cases, since all infants entered the study whilst being ventilated at either 30-40 or 50-60/min. Infants entering at 30-40/min had their rate increased by at least 20/min as a first step. Those entering at 50-60/min were increased to 100/min and then reduced to 30/min as a last stage before returning to their baseline rate.

At 100/min, a second set of recordings were made with the pneumotachograph bias flow switched off. This manoeuvre was performed to enable comparison of the cardiovascular effects of the rate change at different levels of $PaCO_2$. A 12 minute stabilisation period was allowed after each rate change before measurements were made of MABP, CBFV, tidal volume, PIP and PEEP. Even at the fastest rates, the ventilator pressure wave was seen to plateau. At each stage 0.1 ml of blood was taken through the arterial line for $PaCO_2$ and PaO_2 determinations.

6.4(e) Results of Analysis

Parametrical statistical tests were used. Paired t tests were used to compare

observed values of PaO_2, $PaCO_2$, MABP and CBFV at the four ventilator settings. No adjustment was made for multiple comparisons. The principal findings would not have been altered by this adjustment, which was judged unnecessary because of the small number of comparisons being made. Linear regression analysis was used to examine the factors influencing changes in CBFV. A step-down analysis was used, incorporating $PaCO_2$, PaO_2 and MABP as potential explanatory variables. The adequacy of the linear model was checked by plotting residuals.

PaO_2 was little changed at the different ventilator settings, but was just significantly lower at 100/min than at 30/min (p=0.043)(figure 6.1). $PaCO_2$ was significantly lower at 60/min (p=0.0003) and at 100/min (p=0.016) than at 30/min (figure 6.2). With the bias flow turned off at 100/min, however, $PaCO_2$ was not significantly different from that observed at 30/min (p=0.7). There was a substantially higher $PaCO_2$ at 100/min with the bias flow turned off than at the same rate with the pump on (p=0.0036).

There was a slight downward trend in MABP at increasing ventilation rates, which reached borderline statistical significance at 100/min compared with 30/min (p=0.043). Turning the bias flow off at 100/min however, resulted in a clear increase in MABP (p=0.003) relative to the same rate with the pump on (figure 6.3). This did not depend significantly on the accompanying changes in blood gases.

CBFV fell as ventilator rate was increased from 30 to 60/min (p=0.0017), but showed no further fall on further increasing the rate to 100/min (p=0.74). Removal of the bias flow at this rate resulted in a clear rise in CBFV (p=0.008) to the level observed

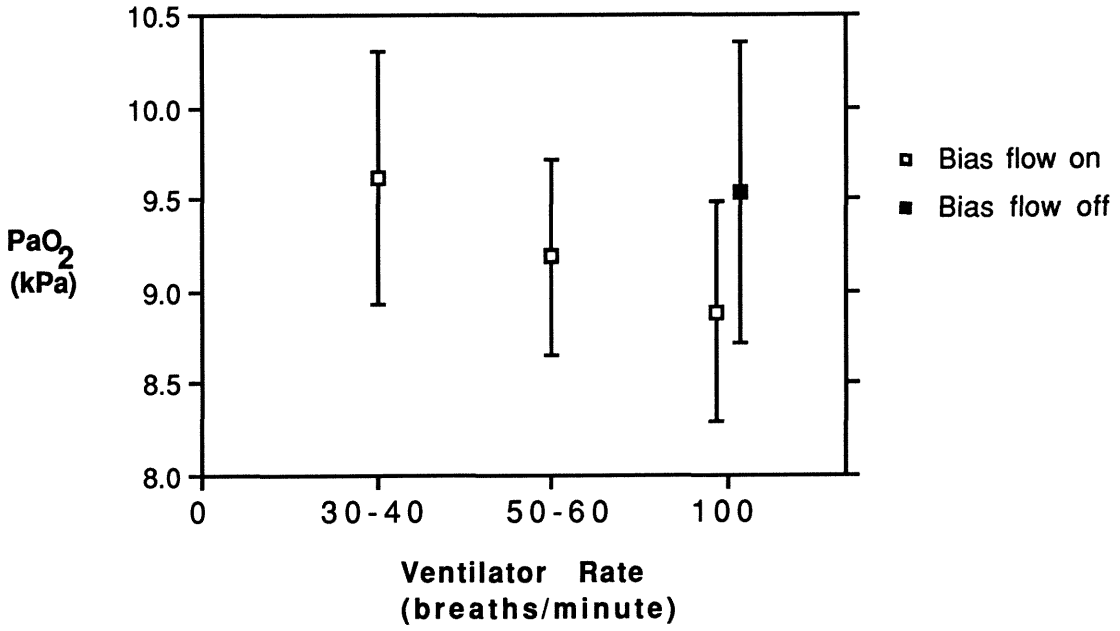

Figure 6.1

Changes in PaO_2 with ventilator rate. Points are mean +/- SEM.

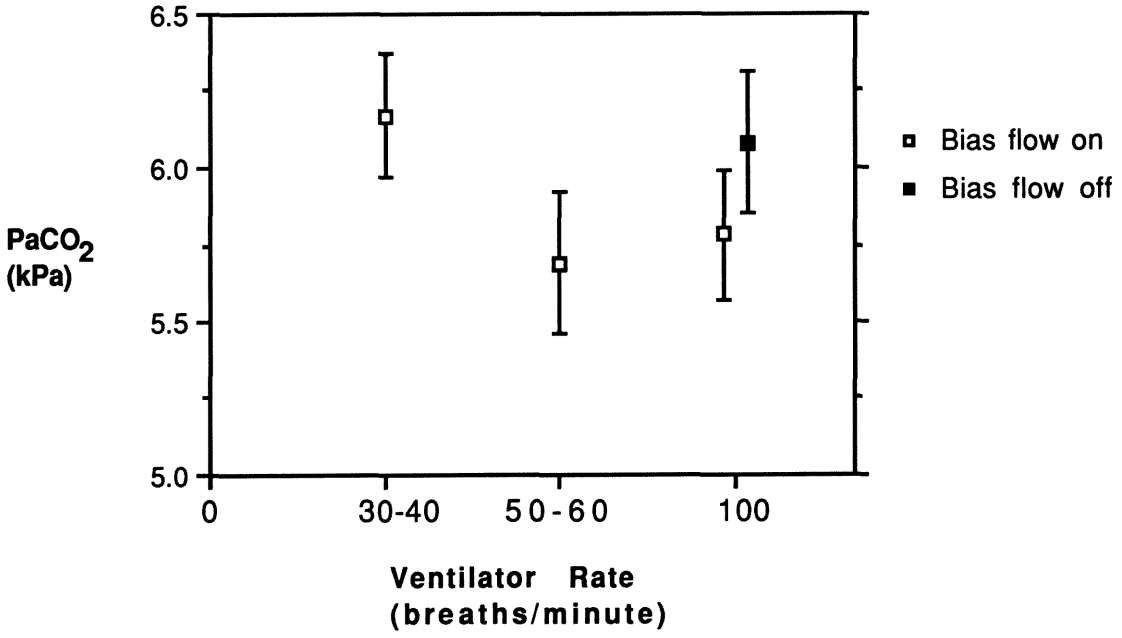

Figure 6.2

Changes in $PaCO_2$ with ventilator rate. Points are mean +/- SEM.

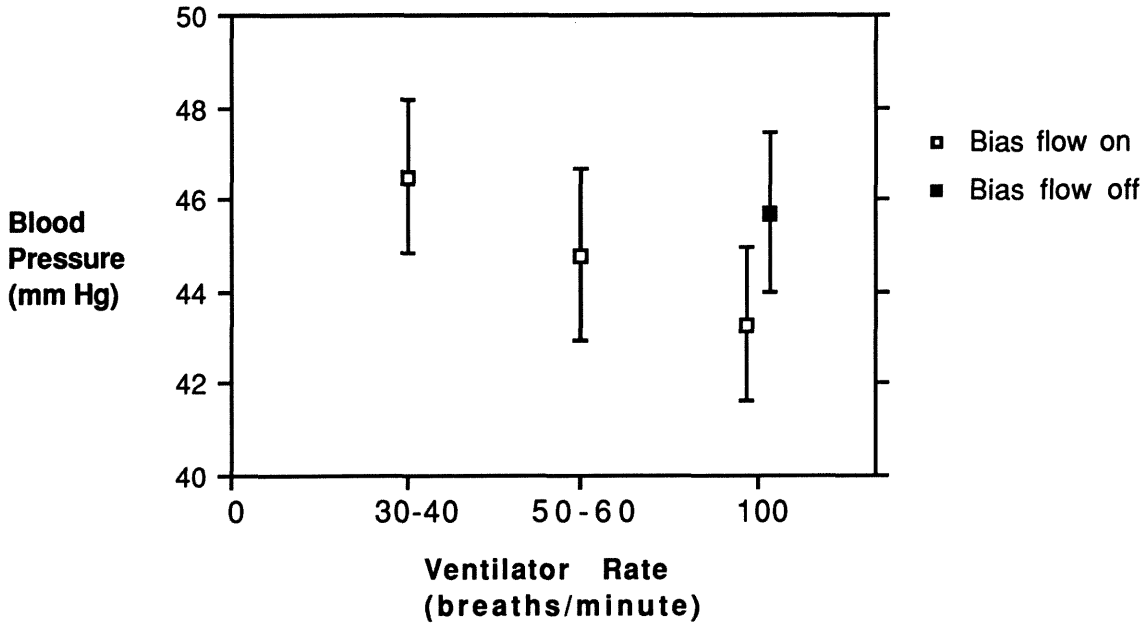

Figure 6.3

Changes in MABP with ventilator rate. Points are mean +/- SEM.

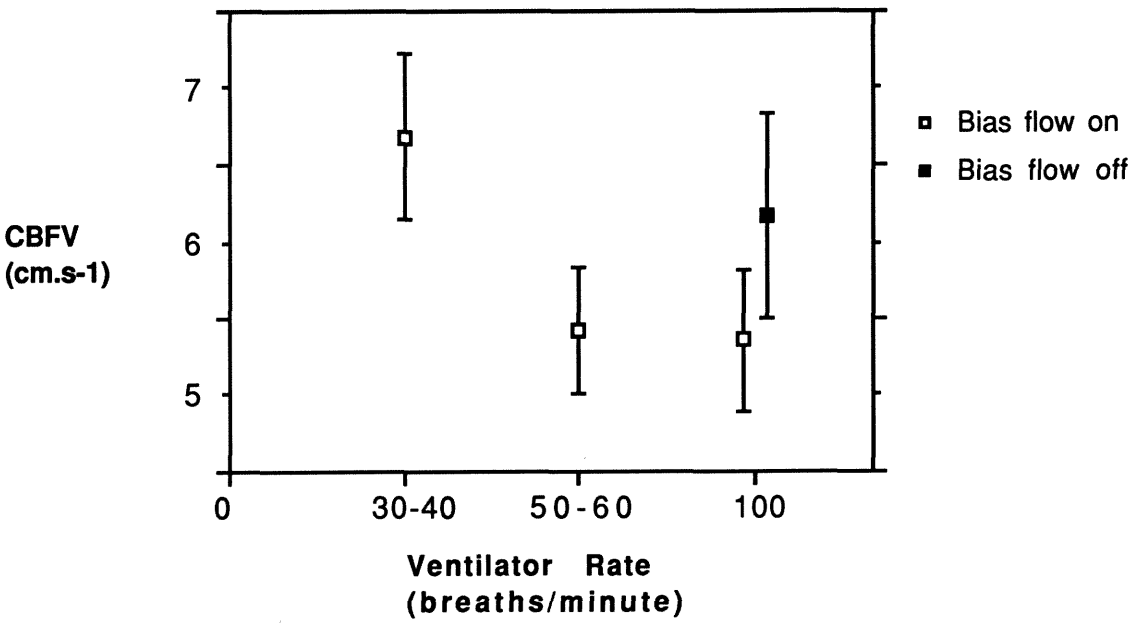

Figure 6.4

Changes in CBFV with ventilator rate. Points are mean +/- SEM.

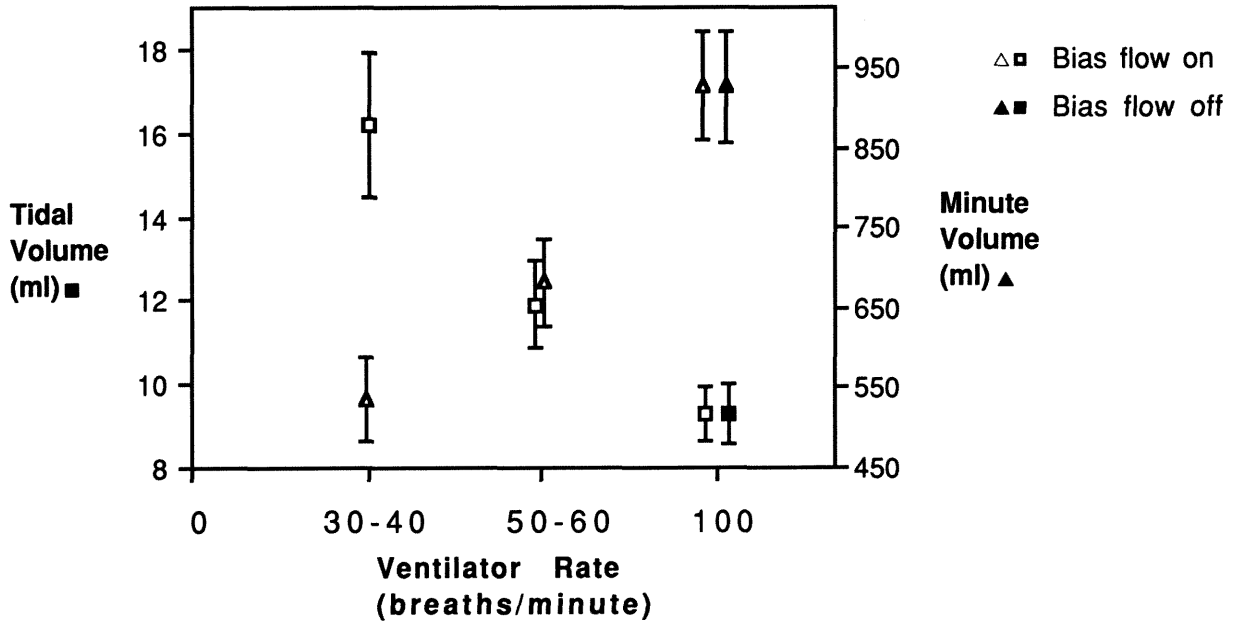

Figure 6.5

Changes in minute and tidal ventilation with ventilator rate. Points are mean +/- SEM.

at 30 breaths per minute (figure 6.4). Stepwise iinear regression indicated that two separate factors were associated with the observed changes in CBFV:

(1) As ventilatory rate was changed from 30 to 100/min, the change in CBFV was closely associated with the change in $PaCO_2$ (p=0.008), but was independent of changes in PaO_2 or blood pressure. The variation in $PaCO_2$ alone was sufficient to account for 30% of the variabiiity in the change in CBFV.

(2) The rise in CBFV on removal of the bias flow at 100/min was not related to the change in $PaCO_2$, but was significantly dependent on the change in MABP (p=0.014). Once the change in MABP had been included in the regression model, the effect of the change in $PaCO_2$ was not significant (p=0.14), as was the effect of the change in PaO_2 (p=0.9). 29% of the variability in the change in CBFV resulting from the removal of the bias flow was attributable to the associated change in MABP.

6.4(f) Discussion

There is relatively little data on the effects of inadvertent PEEP in the preterm infant, which has been shown to occur even at relatively slow ventilator rates (Simbruner 1986). These findings indicate that the use of HFPPV in paralysed infants with stable IRDS does not result in adverse haemodynamic effects or changes in biood gases which might be attributable to inadvertent PEEP.

in a study such as this, standardisation of patients in terms of disease stage is clearly important. The criteria for the use of pancuronium were well defined and ail the infants were studied in a stable state with regard to their ventilatory requirements.

important factors determining the production of inadvertent PEEP are lung compliance and the amount of air leak around the endotracheal tube (Simbruner 1986).

Attempts to measure static compliance were made in all of these infants using a prolonged inspiration technique, but a significant air leak was present in 18 of the infants studied, despite the use of shouldered endotracheal tubes. The two infants in whom successful measurements were made had compliances of 0.5 and 0.6 ml/cm H_2O respectively. As a major leak around the endotracheal tube was present in the majority of the infants studied, it seems likely that this effect limits the tendency to develop inadvertent PEEP. Since the type and size of endotracheal tube used in this study is similar to many neonatal units, it would seem likely that inadvertent PEEP does not pose a clinicaiiy significant problem in paralysed infants.

A potential criticism of the method in view of the air leak is that rather than measuring tidal volumes, changes in air leak aione were being recorded. Whilst this may be true to some extent, the rise in minute volumes recorded (figure 6.5) were accompanied by a concurrent fall in $PaCO_2$ between 30 and 60 breaths per minute, which would not have occurred if the changes measured merely represented alterations in air leak. The subsequent rise in $PaCO_2$ between 60 and 100 breaths per minute despite a further rise in minute volume probably results from the fall in tidal volume at the higher rate (figure 6.5) rendering it less effective.

The significant fall in PaO_2 between slow and fast rates may also be predicted from theoretical principles, since increasing ventilator rate alone (that is producing an increased number of ventilator up-strokes per unit time) will result in a fall in mean airway pressure (MAP), thus directly affecting oxygenation.

These findings are in contrast to those of Greenough et al (1987), who found that the use of HFPPV did not result in significant changes in arterial biood gases. These

findings probably result from methodoiogical differences. Firstly, half of the infants in that study were ventilated with Bourns ventilators which are less efficient at rates of 100/min. Secondly, flow rates were altered to maintain MAP whilst keeping I:E ratios and PiP constant. To do this an increase in PEEP must have been required (not stated in the paper), which would have negated the changes in $PaCO_2$ and PaO_2 which were observed in this study.

The finding that in particular circumstances changes in MABP appeared to exert more influence on CBFV (and thus actual cerebral blood flow; see 3.3e & 4.4f[vii]) than $PaCO_2$ was unexpected. Whilst care must be taken in attaching clinical importance to significant results generated unexpectedly from statistical analysis, the following points are of note:

(1) For this apparent relationship to have resulted from the statistical analysis aione is unlikely, since not only was the significance of the effect of MABP gained, but that of $PaCO_2$ lost.

(2) An effect secondary to the order of rate changes during the study would have been expected to have an opposite effect to that seen.

(3) This effect was observed at levels of $PaCO_2$ encountered at other times in the study and it is therefore unlikely that maximal cerebrovascular dilatation secondary to changes in $PaCO_2$ had been achieved. Were this the case, changes in blood pressure may indeed have had a more prominent influence on cerebral biood flow, resulting in "pressure passive" cerebral blood flow.

(4) This group of infants represent some of the sickest treated in our unit and the apparent dependence of CBFV on MABP may actually represent impaired cerebrovascular regulation. It is however important to bear in mind that $PaCO_2$ acts both by direct and indirect (sympathetically mediated) mechanisms on the cardiovascular system (see 3.3b)

and thus may still be the governing factor in the responses observed. In addition the effect of other factors, for example paralysing agents may have been responsible.

The rise in PaO_2 observed with the bias flow turned off was also unexpected. This too may have resulted from an indirect effect of the change in $PaCO_2$, mediated by changes in MABP. This would in turn raise left atrial pressure and alter shunting at this level. It is interesting to note that none of the surviving infants subsequently developed ultrasound evidence typical of preterm cerebral injury (see 2.2).

6.5 Summary

Previous studies suggest that although various ventilatory modalities may influence cerebral perfusion (through effects on venous return and cardiac output), such effects are small within their usual clinical ranges. Certainly the effects of changes in PEEP are far less significant than those of accompanying changes in $PaCO_2$. The use of HFPPV in paralysed infants does not appear to result in adverse cardiovascular effects which are attributable to inadvertent PEEP. Additionally it results in statistically (though not necessarily clinically) significant changes in arterial blood gases, which would appear to be readily predictable from theoretical considerations. However, under certain conditions, infants ventilated in this way exhibit changes in CBFV which may be to a degree dependent on changes in blood pressure. The use of ventilator rates greater than 50 or 60 breaths per minute in paralysed infants would appear to confer no advantage and may in fact be detrimental. Finally, humoral factors released from the lung as a result of positive-pressure ventilation have not as yet been shown to have a significant effect on cardiac output in vivo.

Having considered the major potential variables which might influence the

cerebrovascular response to a rise in $PaCO_2$, the main question posed in chapter 1 can now be addressed.

Chapter 7

Cerebrovascular Carbon Dioxide Reactivity

7.1 Introduction.

7.2 Patients.

7.3 Study procedure.

- (a) Measurements.
  - (i) Blood pressure.
  - (ii) Cerebral blood flow velocity.
  - (iii) Ventilatory parameters.
- (b) CO_2 challenge.
  - (i) Method.
  - (ii) Reproducibility.
- (c) Real-time ultrasound.

7.4 Analysis.

7.5 Results.

- (a) Baseline parameters.
- (b) The response to increased $PaCO_2$.
- (c) Inter-relationship of factors in the CO_2 response.
- (d) Effects of pancuronium.

7.6 Predictive value of the CO_2 response.

7.7 Discussion.

7.8 Summary.

Hypothesis: The change in CBFV following a 1 kPa rise in $PaCO_2$ predicts susceptibility to the subsequent development of PVL in ventilated preterm infants.

7.1 Introduction

Literature relating to the cerebrovascular response to changes in $PaCO_2$ has previously been reviewed (see 3.3b). Essentially, a rise in $PaCO_2$ causes a rise in cerebral blood flow secondary to arteriolar dilatation. Levene et al (1988) showed that the majority of very immature infants increased their CBF (as assessed by a rise in CBFV) in response to a rise in $PaCO_2$ of approximately 1 kPa. A subgroup however showed the opposite effect. In 6 out of 19 infants studied there was a fall in CBFV following the rise in $PaCO_2$. Of these 6 infants, 3 subsequently developed PVL, whereas all of the remaining infants, who showed either no change or a rise in CBFV, had normal cranial ultrasound appearances. it was felt unlikely that the induced rise in $PaCO_2$ had itself caused the PVL, since the $PaCO_2$ was not changed outside of the normal range and a change of 1 kPa is probably representative of normal daily fluctuations in infants being ventilated for iRDS. A similar CO_2 "challenge" might thus be used to assess the integrity of the cerebral circulation in ventilated preterm infants and be of value in predicting those infants at risk of developing PVL. The following study examined the effects of a similar change in $PaCO_2$ on a large group of preterm infants being ventilated for iRDS.

7.2 Patients

All infants of ≤34 weeks gestation who were ventilated at Leicester Royal infirmary for IRDS were considered eligible for the study. infants were not studied if their condition was considered unstable, if their initial $PaCO_2$ was >7 kPa, if there was no in-dwelling arterial line or if there were cranial ultrasound abnormalities at the time of

their first study. Infants were studied as soon as possible after birth and daily thereafter until extubation.

During the study period, 104 infants of suitable gestational age were ventilated for IRDS. Of these, one was excluded because of multiple congenital abnormalities, including microcephaly. Three infants died within the first two days of life without being studied, as their condition was judged to be too unstable. CBFV recordings from four infants were unable to be analysed for technical reasons and two infants referred from other hospitals had existing cranial ultrasound abnormalities at the time of referral. The remaining 94 infants were studied on a total of 382 occasions. Their gestational age ranged from 25 to 34 weeks and postnatal age from 2 to 335 hours. Individual clinical and study details are given in Appendix 3. 82 infants were studied on at least 2 occasions and the first study was performed at a mean of 15.6 hours after birth.

7.3 Study Procedure

(a) Measurements

Prior to each study the following parameters were recorded:

(i) Blood Pressure

Blood pressure was measured as previously described (6.4c[i]). A permanent record of blood pressure was made on a chart recorder (Gould) and mean arterial pressure (MABP) noted.

7.3a(ii) Cerebral Blood Flow Velocity

In all infants, CBFV recordings were made from one ACA using an ATL 600 duplex Doppler system (see 5.3a[i]) on to digital audiotape and analysed as described in 5.3a(ii), the same precautions being observed with regard to the angle of insonation of the vessel and adjustment to obtain the optimum signal.

7.3a(iii) Ventilatory Parameters

Ventilator settings and whether the infant was paralysed with pancuronium at the time of the study were recorded. Prior to each study, 0.2 ml of blood was taken from the infant's arterial line for $PaCO_2$ and PaO_2 determinations. Routine sedation with an opiate was not used during the course of this study.

7.3(b) CO_2 Challenge

(i) Method

In order to raise the $PaCO_2$, a piece of non-compliant tubing (internal diameter 12 mm, length to give volumes between 5 and 12.5 ml, depending on the size of the baby being studied) was placed in the ventilator circuit between the ventilator manifold and the end of the infant's endotracheal tube. This acted as a "dead-space", causing $PaCO_2$ to rise. A potential problem with this arrangement is that the dead-space might increase the resistance of the ventilator circuit. For this reason measurement of the resistance of the dead-space tubing was made.

The resistance (R) of any tube is determined by the flow rate (V) and the pressure drop (P) along its length and may be expressed by the following equation:

$$R = P / V \qquad [6]$$

For these measurements, the maximum possible contribution to resistance relative to that of the endotracheal tube that a dead space could make was determined. This was achieved by combining the longest dead space (that with potentially the largest

resistance) and the largest internal diameter endotracheal tube used for the infants studied (the lowest resistance).

Gas flows likely to be encountered at the ventilator manifold in the infants studied were estimated in the following manner. The largest tidal volumes achieved were up to 20 ml (see figure 6.5 & Appendix 2). The major part of this volume is delivered by the ventilator in about 0.3 seconds (Field DJ, unpublished data), and therefore the maximum possible flow rate (litres.min^{-1}) can be calculated as follows:

$$\text{Flow rate} = \text{volume/time} \qquad [7]$$
$$= 20/0.3$$
$$= 66.67 \text{ ml.s}^{-1}$$
$$= 4 \text{ l.min}^{-1}$$

Oxygen was passed through a rotameter to achieve steady flows both greater and less than this calculated flow before being passed through either the endotracheal tube alone or combined with the dead space. The endotracheal tube was open to atmosphere at its distal end. The pressure gradient along the tube could therefore be determined using a spinal needle attached to a pressure transducer inserted into the system just proximal to the endotracheal tube (figure 7.1). Pressure changes were recorded on a storage oscilloscope and subsequently plotted off-line.

Knowing flow rate and pressure gradient, resistance (cm $H_2O.l^{-1}.s$) may be calculated. Resistance was then plotted against flow rate (figure 7.2) and it can be seen that in the inspiratory phase, the dead-space resistance is <2% of the resistance of the endotracheal tube. This occurred at the highest flow rates used (7.4 l.min^{-1}) and was

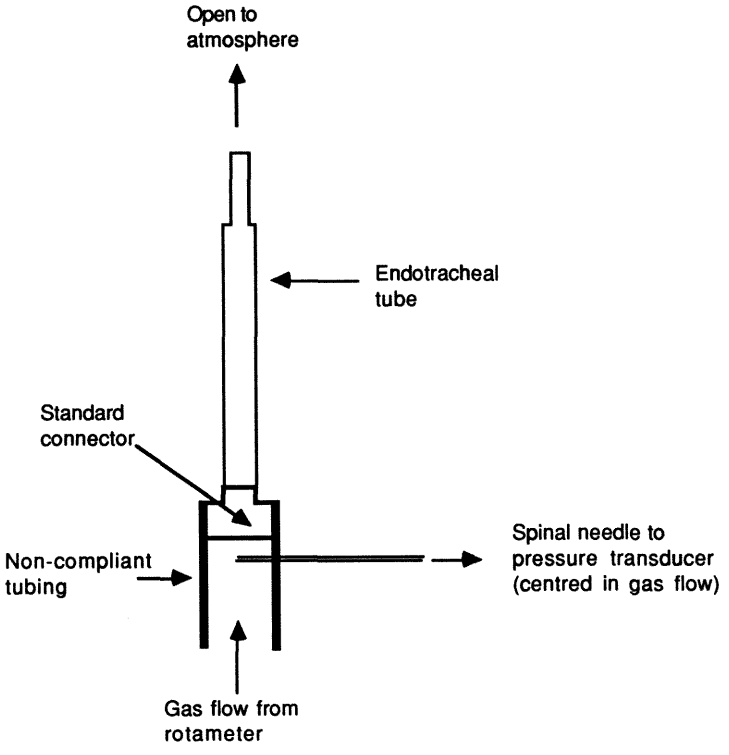

Figure 7.1

Apparatus for determining resistance of endotracheal tube +/- dead space.

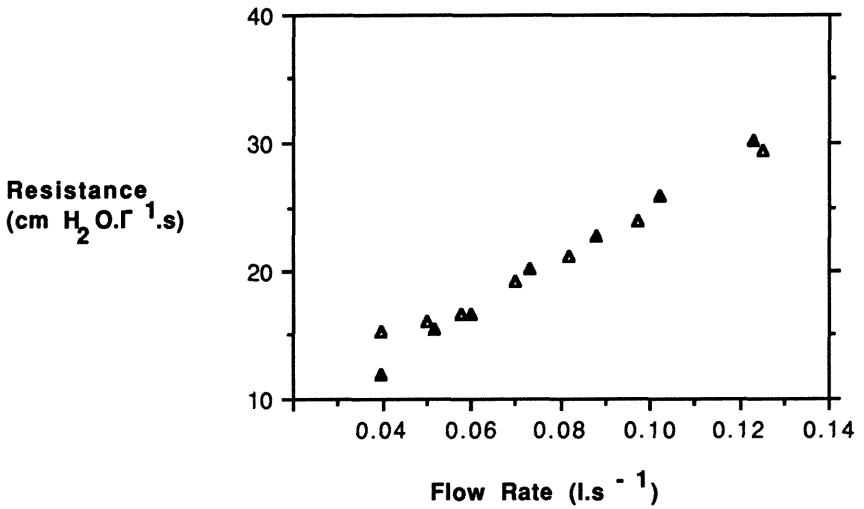

Figure 7.2

Resistance of 3.0 mm endotracheal tube with (shaded symbols) and without (open symbols) 12.5 ml dead space. Plot shown represents inspiratory phase (ie oxygen passed from rotameter through dead space and thence into endotracheal tube).

even less at flow rates likely to be found at the ventilator manifold, making accurate determination difficult. Dead-space contribution to resistance during expiration was also negligible.

To confirm that the use of such a deadspace did not affect the ventilator pressures being delivered, airway pressure was measured using a butterfly needle inserted into the endotracheal tube, attached to a pressure transducer (Spectramed P23XL). The $PaCO_2$ was then allowed to equilibrate for 10-15 minutes, the change being monitored where possible by a transcutaneous CO_2 electrode. A further 0.2 ml of blood was taken for repeat blood gas analysis, and then repeat MABP and CBFV recordings were made as before.

7.3b(ii) Reproducibility

Repeating each study on every infant to examine the reproducibility of the results would have entailed extra handling and the taking of extra blood samples, which clearly could not have been justified. However, in 10 infants the study was repeated after an interval of between 30 and 90 minutes. The changes in CBFV and MABP on each occasion were standardised for a 1kPa rise in $PaCO_2$ (table 7.1). Reproducibility of the result for the paired responses was assessed using the method of Bland and Altman (1986). The mean and standard deviation (SD) of the difference between the two values obtained for both the CBFV and MABP response to the rise in $PaCO_2$ were determined. For the change in CBFV the mean difference between the responses obtained (table 7.1; [a-b]) was 0.1 $cm.s^{-1}$ (SD=0.06) and for the change in MABP (table 7.1; [c-d]) the mean difference was 0.36 mm Hg (SD=0.33). In addition, the difference between the two values obtained from each individual was divided by their mean, and expressed as a percentage. The mean percentage difference between replicate readings for the group as a whole was 7.12% for the change in CBFV and 12.06% for the change in MABP. These results indicated

Infant	Study 1 ΔPaCO$_2$ (kPa)	ΔCBFV (cm.s^{-1})	ΔCBFV / ΔPaCO$_2$	ΔMABP (mm Hg)	ΔMABP / ΔPaCO$_2$	Study 2 ΔPaCO$_2$ (kPa)	ΔCBFV (cm.s^{-1})	ΔCBFV / ΔPaCO$_2$	ΔMABP (mm Hg)	ΔMABP / ΔPaCO$_2$	(a)-(b) / 0.5{(a)+(b)} (%)	(c)-(d) / 0.5{(c)+(d)} (%)
a	0.87	1.5	1.72	4	4.60	0.84	1.5	1.79	4	4.76	3.99	3.42
b	1.13	1.0	0.88	5	4.42	0.63	0.5	0.79	3	4.78	10.78	7.41
c	1.14	1.0	0.87	2	1.75	1.64	1.5	0.91	3	1.83	3.35	4.47
d	1.22	1.5	1.23	1	1.12	0.89	1.0	1.12	1	1.12	9.36	30.92
e	0.97	0.5	0.52	2	2.06	1.04	0.5	0.48	3	2.88	8.00	33.20
f	0.53	1.0	1.89	4	7.55	0.75	1.5	2.00	5	6.67	5.66	12.38
g	1.32	1.5	1.14	3	2.27	1.25	1.5	1.20	3	2.40	5.13	5.57
h	1.11	2.0	1.80	6	5.41	0.93	1.5	1.61	5	5.38	11.14	0.56
i	0.74	1.0	1.35	2	2.70	0.77	1.0	1.30	2	2.60	3.77	3.77
j	0.87	2.0	2.30	3	3.45	0.96	2.0	2.08	4	4.17	10.04	18.90
			(a)		(c)			(b)		(d)		
											mean = 7.12%	*mean* = 12.06%

Table 7.1

Reproducibility of changes in CBFV and MABP induced by a standardised 1 kPa rise in PaCO$_2$.

satisfactory reproducibility within the time scale of the studies.

7.3(c) Real-time Ultrasound

The use of real time ultrasound scanning in neonatal practice and the correlation of ultrasound appearances with pathological findings has already been discussed (see 2.2). All infants studied had real-time brain scans performed:

(1) At the time of each study.

(2) Following extubation twice weekly for the first two weeks.

(3) Subsequently once each week until discharge.

Scans were classified as reported by Trounce et al (1986a): either normal, or showing haemorrhage and/or PVL, the latter being subdivided into prolonged flare or cystic degeneration (see 2.2).

7.4 Analysis

The results for each day of life were analysed separately using linear regression to examine the factors influencing changes in CBFV for a standardised change in $PaCO_2$ of 1 kPa. A step-down analysis was used, incorporating MABP, heart rate and PaO_2 as potential explanatory variables. The adequacy of the linear model was checked by plotting residuals. Mann-Whitney tests were used to compare changes in these variables in infants with and without subsequent cranial ultrasound abnormalities. The effect of gestational age on these differences was also examined. Longitudinal analysis (within-subject) was performed using paired t tests to compare changes in CBFV, MABP and PaO_2 with the lower and higher $PaCO_2$ values at different postnatal ages. No adjustment was made for multiple comparisons. The principal findings would not have been altered by this adjustment, which was judged unnecessary because of the small number of comparisons being made.

The effects of gestational age was assessed by dividing the infants into two groups: those ≤30 weeks and those ≥31 weeks.

7.5 Results

The following changes were observed in the first week of life:

(a) Baseline Parameters (figures 7.3 & 7.4)

Mean baseline CBFV and MABP rose by 46% (2 $cm.s^{-1}$) and 11% (4 mm Hg) respectively between the first and second days of life ($p<0.001$, $p=0.01$ respectively). MAP rose by a further 10% (4 mm Hg) over the subsequent 24 hours ($p=0.001$). Baseline $PaCO_2$ changed iittle throughout the first week, with somewhat larger day to day variations in PaO_2. CBFV was not affected by gestation, but MABP was significantly higher in infants ≥31 weeks compared to those ≤30 weeks ($p=0.01$) throughout the first week.

7.5(b) The Response to increased $PaCO_2$ (tabie 7.2)

The mean induced change in the $PaCO_2$ remained relatively constant from day to day. The mean rise in CBFV (for a standardised rise in $PaCO_2$ of 1 kPa) was 1.1 $cm.s^{-1}$ (SEM 0.3) during the first 24 hours after birth. This represented a mean increase of 33% from baseline CBFV ($p<0.001$). During the subsequent 24 hours, the mean rise in CBFV was 2.1 $cm.s^{-1}$ (SEM 0.4) which was significantly greater (53%, $p=0.001$). Overall, CBFV rose on 322 occasions, fell on 35 occasions (28 infants) and showed no change on 25 occasions (21 infants). No infant showed a fall in CBFV on every occasion studied. The CBFV response was not influenced by gestational age.

Overall, the change in MABP was highly significant ($p<0.001$), rising on 281 occasions, failing on 74 occasions (53 infants) and showing no change on 27 occasions (24 infants). The mean rise in MABP was less during the first 24 hours of life (1.5 mm Hg,

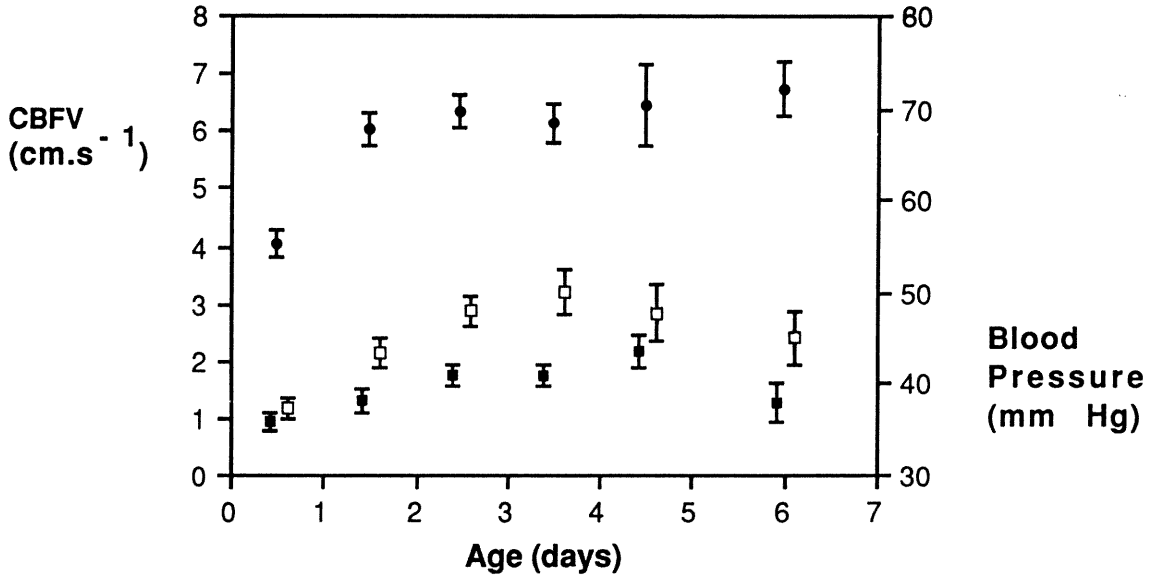

Figure 7.3

Changes in baseline blood pressure (□ infants ≥31/40, ■ infants ≤30/40) and CBFV (●) over the first week of life. Points are mean +/- SEM.

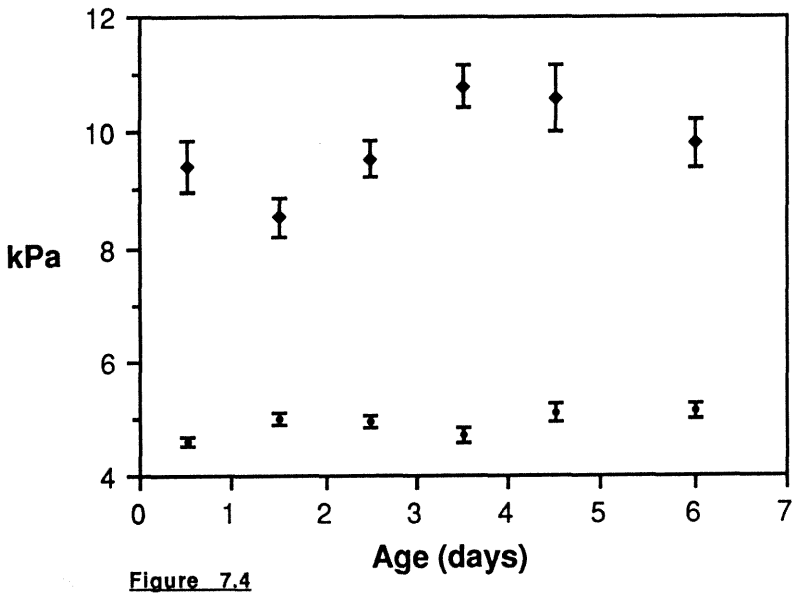

Figure 7.4

Changes in baseline PaO_2 (◆) and $PaCO_2$(●) over the first week of life.
Points are mean +/- SEM.

Age (days)	1	2	3	4	5	6 - 7
$\Delta PaCO_2$ (kPa)	1.1	1.2	1.1	1.2	0.9	1.1
$\Delta CBFV/\Delta CO_2$ (%)	33 *	53	49	55	52	51
$\Delta MABP/\Delta CO_2$ (%)	5.2 †	7.6	7.7	8.1	8.6	8.6

(*) p=0.001 (†) p=0.04

Table 7.2

Mean rise in $PaCO_2$ induced and resulting percentage rises in CBFV and MABP (all infants). Statistical analysis refers to days 1 & 2.

SEM 0.4) compared to subsequent days (2.4 mm Hg, SEM 0.5), but was unaffected by gestation. The fall in MABP was accompanied by a fall in CBFV on 12 occasions in 11 infants, all of whom were ≤30 weeks. On the other occasions when MABP fell, CBFV either remained constant or rose. This occurred in infants of all gestations.

Accompanying significant changes in PaO_2 occurred (mean rise 1.7 kPa, SEM 0.6) in the first 24 hours ($p=0.006$), but thereafter were not significant. This response was also unaffected by gestation.

7.5(c) Inter-relationship of Factors in the CO_2 Response

Factors affecting the CBFV response to the rise in $PaCO_2$ varied with both postnatal and gestational age. For infants ≤30 weeks, during the first 24 hours after birth the change in CBFV in response to the rise in $PaCO_2$ depended significantly on the accompanying changes in MABP ($p<0.001$, regression coefficient 0.69, SD 0.12) to which 53% of the variability (coefficient of determination, R^2) in CBFV was attributable (changes in $PaCO_2$ and PaO_2 being included in the regression model). This relationship was not significant after the first 24 hours in these infants, or for infants ≥31 weeks both during and after the first 24 hours.

7.5(d) Effects of Pancuronium

There were 31 infants in the group who received pancuronium to facilitate ventilation after they had been studied on at least one occasion. Of these, 22 had at least two studies whilst paralysed and at least one further study performed after stopping pancuronium. The decision to use pancuronium was made independently by the clinicians responsible for the infants' care. Their gestational ages were representative of the study group as a whole, as were their baseline values of CBFV, MABP, $PaCO_2$ and the CBFV and

MAP responses to the rise in $PaCO_2$.

Analyses were performed as previously, comparing the infants' response to the rise in $PaCO_2$ prior to administration of pancuronium (mean postnatal age 10 hours), whilst paralysed (mean ages 41 and 65 hours) and after stopping paralysis (mean age 119 hours). Prior to paralysis, changes in CBFV following the rise in $PaCO_2$ were not significantly dependent on MABP, regardless of gestation. Following administration of pancuronium, however, changes in CBFV were dependent on MABP ($p=0.015$, regression coefficient 0.84, SD 0.31), with 28% of the variability in CBFV due to changes in MABP. This dependence persisted for the duration of paralysis ($p=0.014$), but was not significant following cessation of paralysis. This was independent of gestation.

7.6 Predictive Value of the CO_2 Response

27 infants (28%) developed mild intraventricular hemorrhage and a further 4 had severe hemorrhage with parenchymal involvement. 21 infants (22%) had prolonged flare on cranial ultrasound, of whom 9 (9.6%) subsequently developed cystic changes. One further infant developed a single small periventricular cyst without preceding flare. The change in CBFV did not predict subsequent development of haemorrhage ($p>0.21$), prolonged flare ($p>0.33$) or cystic PVL ($p>0.36$), even in gestational age subgroups.

7.7 Discussion

Studies involving the effects of carbon dioxide on the circulation are beset with difficulties, with important ethical and methodological considerations, concerning the degree of $PaCO_2$ manipulation and the way in which this is achieved respectively (see 3.3b[ii]). The method used here allowed a significant change in $PaCO_2$ to be made (whilst remaining within the normally accepted range) and achieved a steady state at the higher

level rapidly and consistently, without the need to adjust ventilator settings. The latter method will have direct effects on PaO_2, which may be detrimental to the infant in addition to potential (although probably not clinically significant) secondary effects on cardiac function (see chapter 6). The question of whether changes in CBFV measured from a major vessel such as the ACA represent changes in actual CBF has already been addressed (see 3.3e and 4.4g), and the use of Doppler velocimetry in this particular situation would seem valid.

The characteristics of the infants studied are representative of the populations seen in most neonatal intensive care units. Mean baseline values of CBFV and MABP (figures 7.3 and 7.4) are comparable with published normal ranges (Evans et al 1988, Shortland et al 1988). The 46% rise in baseline CBFV between the first and second days did not appear to be due to the concomitant 11% rise in baseline blood pressure ($p=0.8$) and further rises in blood pressure later in the first week were not associated with significant changes in baseline CBFV.

The factors on which the changes in CBFV in response to the rise in $PaCO_2$ depended altered significantly with both gestation and postnatal age. These data indicate that in the first 24 hours after birth, extremely preterm infants (≤30 weeks gestation) demonstrate changes in CBF in response to a rise in $PaCO_2$ which are dependent to a great extent on concomitant changes in blood pressure. They are therefore potentially at greater risk from sustaining ischaemic injury than their more mature counterparts. The mechanisms responsible for this difference remain unclear. The transition to extra-uterine life most obviously entails loss of the placental circulation, which in utero tends to damp down circulatory changes due to variations in fetal cardiac output (Nuwayhid et al 1975). Following birth, if vasomotor tone is insufficiently mature, changes in blood

pressure may directly affect organ blood flow. Reasons for the loss of this pressure passivity in the less mature infants after the first 24 hours are also unclear. However, whilst neurogenic and humoral mechanisms are thought to play a relatively minor role in the regulation of cerebral blood flow under normal circumstances, under conditions of stress and in the presence of immature vasomotor tone (Haruda & Blanc 1981) they may have a more influential role (see 3.3b & 3.3d). In addition the catecholamine surge around the time of birth has been shown to influence the behaviour of receptors in lung tissue (Walters & Olver 1978, Brown et al 1983) and similar responses may well be induced in other tissues, such as the brain.

Similarly, involvement of neurogenic and humoral factors may be responsible for the changes observed following administration of pancuronium. Roizen et al (1979) demonstrated that administration of pancuronium resulted in a fall in plasma noradrenaline levels in adults, which they felt resulted from a generalised reduction in sympathetic outflow. There is however conflicting evidence in this area, since others have demonstrated both a direct and an indirect sympathomimetic response to the administration of pancuronium (Docherty & McGrath 1978, Domenach et al 1976).

From the results of the ventilator rate study (see 6.4[e]), it appeared that paralysed infants demonstrated pressure passive changes in CBFV at fast ventilator rates, when the $PaCO_2$ was raised using a deadspace. However, this higher $PaCO_2$ level was not significantly different from that when the infants were ventilated at slow rates, yet at the slower rate CBFV was not blood pressure dependent. It may be that the loss of autoregulation to a $PaCO_2$ challenge which was found in those infants was not a function of fast ventilator rates as suspected, but rather was related to the use of pancuronium. These findings of a potential adverse effect of pancuronium in terms of preterm cerebral injury contrasts with previous work by Perlman et al (1985c and see 6.3) which suggested a

beneficial effect in terms of development of intraventricular hemorrhage. The authors suggested that this resulted from reduced variability in blood pressure, which in turn arose from the infant's interraction with the ventilator. Clearly caution must be exercised in attaching clinical significance to an unexpected finding on statistical analysis, but these results suggest that the effects of pancuronium in the preterm neonate warrant further study.

Whilst these results are also comparable with those of Levene et al (1988), they are at variance with those of Pryds et al (1989). Using an intravenous ^{133}Xenon technique to measure cerebral blood flow, they found a large increase in the change in flow for a standardised rise in $PaCO_2$ between the first and second days of life (11.5 and 32.6% respectively), though again the numbers studied on two occasions were small. These values are lower than others have found using a similar method for assessing cerebral blood flow (Greisen & Trojaborg 1987). Baseline $PaCO_2$ rose significantly between the first and second days and the absolute change in $PaCO_2$ used (+/-0.5 kPa) before standardisation to 1 kPa was smaller than in this study, and was achieved by unspecified "ventilator manipulation". in view of the potential effects on cardiac output and hence blood pressure that such manoeuvres might engender, it is interesting to note that no specific $PaCO_2$-blood pressure relation was noted. Finally, ail the infants in that study were paralysed with pancuronium. Clearly the potential effects suggested here in association with pancuronium may have influenced their results. In addition, all of the infants in their study received phenobarbitone as part of their management and although conflicting evidence exists, the use of barbiturates may well affect the cerebrovascular CO_2 response, mediated by an effect on brain metabolic rate (see 3.4b[v]).

Wyatt et al (1991) reported a linear increase in the cerebrovascular response to

changes in $PaCO_2$ with gestation in 17 ventilated infants, a relationship which was not found in the present study. Only 10 of their cohort were ≤32 weeks, each infant being studied on one occasion. The change in $PaCO_2$ was achieved by adjustment of ventilator rate. The mean baseline $PaCO_2$ for the group was 6.2 kPa (range 3.9-9.6 kPa) and the change induced (0.5-1.8 kPa) was either an increase or a decrease, depending on the baseline value. Whether any infants received pancuronium was not stated. Clearly these factors make further comparison with the present study difficult.

Direct comparison of data from sick preterm infants with that obtained from either fit awake volunteers or anaesthetised adults is also difficult. These data are in agreement with previous work suggesting that the preterm cerebrovascular response to a rise in $PaCO_2$ is greater than the attenuated response of newborn term animals (see 3.3b[v]). This may reflect the difference between the lower vascular density compared to the adult in the newborn term animal and the degree of poor cerebrovascular control relative to term in the preterm group. However, the corresponding rise in MABP (approximately 1% per mm Hg rise in $PaCO_2$) is very similar to that found in awake adult volunteers (0.9% per mm Hg rise in $PaCO_2$; Cullen & Eger 1974).

The failure of the CO_2 "stress" to identify infants who subsequently developed ultrasound evidence of PVL may have been due to several factors. Firstly, all infants were studied when stable, and thus the CO_2 response would have been unaffected by the acute clinical problems to which development of PVL has been shown to be related (see 2.3). This is unlike the fixed alteration in the CO_2 response that occurs in adults with cerebrovascular disease (see 3.3b[vi]). Secondly, although studies were performed during periods when the infants were inactive, no formal assessment of sleep state was

made, which may have influenced baseline CBFV. Thirdly, the cyclical variability of CBFV (1.5-5 cycles/minute with a median change of 23% in systolic velocity) in both sick and healthy infants described by Anthony et al (1991) using on-line Doppler apparatus as described in 5.3(b) may have influenced the degree of change in CBFV following the rise in $PaCO_2$. Similar cyclical variability of cerebral blood volume (3 cycles/minute) has also recently been reported in one preterm infant by Livera et al (1992) using near infrared spectroscopy and venous occlusion plethysmography. Anthony et al suggested that the most likely mechansim for this pattern (which has not been documented in adults) is immaturity of cerebrovascular autoregulation. Lastly it has been assumed that the changes observed on ultrasound represent the end result of postnatal events alone on an immature brain with incomplete development of vascular control, and as discussed in chapter 2 some may result from antepartum events.

7.8 Summary

The degree or nature of the cerebrovascular response to a rise in $PaCO_2$ in ventilated preterm infants does not predict subsequent PVL identified on ultrasound. However, the findings that changes in CBFV following changes in $PaCO_2$ are greatly influenced by accompanying changes in blood pressure both in infants ≤30 weeks gestation within the first 24 hours after birth and in infants following administration of pancuronium have important implications. Since such pressure-dependence of flow has been linked to subsequent neurodevelopmentai injury, it is clearly important that accurate, continuous monitoring of blood pressure and avoidance of large pressure changes is carried out in these potentially at-risk infants.

From these results and those presented in the previous chapter it appears that certain circumstances render cerebral blood flow in ventilated preterm infants

potentially dependent on arterial blood pressure. Clearly then factors which influence blood pressure warrant further consideration.

Chapter 8

Cardiovascular Considerations

8.1 Assessment of cardiac output.

(a) Introduction.

(b) Thermodilution versus Doppler (1).

(i) Thermodilution.

(ii) Doppler.

(iii) Other methods.

(c) Thermodilution versus Doppler (2).

(i) Introduction.

(ii) Patients.

(iii) Study procedure.

(iv) Statistical analysis.

8.2 Cardiovascular effects of CO_2 in ventilated preterm neonates.

(a) Patients and methods.

(b) Statistical analysis.

(c) Results.

(d) Discussion.

8.3 Summary.

8.1 Assessment of Cardiac Output

(a) Introduction

From the results of the studies presented in chapters 6 and 7, blood pressure would appear under certain conditions to have a major influence on CBF in ventilated preterm infants. Clearly then an understanding of factors influencing ABP following a

change in $PaCO_2$ is important.

Blood pressure is the product of peripheral resistance and cardiac output. There is no method avaiiable for quantitative non-invasive assessment of components of overall vascular resistance such as the renal and mesenteric beds and any such measurements in the neonate would be further complicated by the small size of vesseis involved.

Measurement of cardiac output, the "ultimate expression" of cardiac function aiso presents difficuities both in method and in the interpretation of the results obtained if it is measured relativeiy infrequentiy. The determination of "absolute" cardiac output in isolation without consideration of factors inciuding myocardiai contractiiity (itself affected by neuroendocrine factors), pre- and after-load is probably of little clinical use, though this view is not shared by all (Singer et al 1989). Of more reievance wouid be a simpie, safe and reiiable method of assessing changes in output, for exampie in response to therapeutic manoeuvres.

8.1(b) Thermodilution versus Doppler (1)

Techniques based on the Fick principle (see 4.4[a]) such as thermodiiution are regarded as the "gold standard" by which other methods are to be judged, but have several problems related to their use in general and in particular to the neonatal setting (see 8.1b[i]). Doppler ultrasound techniques have been compared with thermodilution in both the adult and paediatric literature as a non-invasive method of assessing cardiac output. These studies and the problems relating to these and other methods will now be reviewed.

8.1b(i) Thermodilution

This technique relies on the temperature change in a bolus of cold fluid measured using a thermistor distal to the site of injection. in the adult situation the

injection is generally made in the right atrium, the thermistor being placed in the pulmonary artery.

In general terms, a major source of error with this method arises from the pulsatile nature of cardiac output, there being less variability results obtained in artificial circulations when assessing non-pulsatile flow (MacKenzie et al 1986). In addition there are difficulties in terms of the amount of thermal indicator lost before entry into the circulation (Maruschak et al 1982) and also from the circulation via the vessel walls. The intrathoracic temperature may vary firstly because of phasic heat exchange with the lungs, and also because of variability in the return of cooler blood from the periphery. These problems may be reduced by using room temperature injectate, but this has the disadvantage of being less accurate than using cold solutions. In addition, the volume of injectate used must be balanced against the need to ensure an adequate temperature change to be detected. Cardiac output itself will also vary with the respiratory cycle and finally large differences may apparently arise depending on the type of equipment used (MacKenzie et al 1986). In terms of assessing changes in cardiac output, it has been estimated that a change of at least 12-15% (using 3 thermodilution determinations for each output) is required to suggest a clinically significant change (Stetz et al 1982).

Several problems relate more specifically to the use of this technique in sick preterm infants. Firstly, it is time-consuming and requires the insertion of a pulmonary artery catheter. Secondly, injection of not inconsiderable volumes of fluid (in the neonatal setting) must be made. Thirdly, overestimation of cardiac output occurs at low stroke volumes and fast heart rates (Berman et al 1988). These reasons render it unsuitable for use in sick neonates, especially if repeat measurements are to be performed over a period of time.

7.1b(ii) Doppler

Doppler techniques for estimation of cardiac output rely on estimating the velocity of blood in the ascending aorta, using similar methods to those described previously (see 4.4[g]). The pulsatile nature of cardiac output lends itself well to Doppler assessment, contrasting with thermodilution (see 8.1b[i]). Doppler assessment of cardiac output compared favourably with electromagnetic flowmeters in thoracotomised dogs (Steingart et al 1980). The main sources of error were considered to be due to systolic turbulence, and of high frequency, low amplitude components "riding" on lower frequency components, thus escaping detection. In addition, transducer movement introduced low frequency noise, and lower stroke volumes were overestimated by the Doppler. The gain requirements for using the same system without thoracotomy might also introduce low frequency, high amplitude sound. Most of these frequency problems can be overcome using Fourier analysis (see 5.2[d]). The main sources of error using a Doppler technique are as follows.

Firstly, the angle of insonation should be minimised (see 4.4[g]). Alverson et al (1982) used a suprasternal approach to minimise this angle in a group of neonates and children. Cardiac output estimations by this method which used stroke distance and aortic cross-sectional area (CSA) compared well with a Fick method at cardiac catheterisation.

Other similar studies of various paediatric populations under a variety of conditions (ihlen et al 1984, Walther et al 1985, Scholler et al 1986, Notterman et al 1989) have obtained varying degrees of correlation with Fick methods. They have all utilised non-imaging Doppler equipment, relying on identification of characteristic waveforms from the great vessels and then adjusting transducer alignment to obtain the optimum signal. It should be noted that the velocity profile may vary across the width of the vessel and therefore sampling from the middle of the vessel may not reflect mean flow

(see 5.2f[i]). Animal studies however have demonstrated that in the ascending aorta a centre-line flow velocity measurement may be used as representative of the mean velocity, due to the blunted velocity profile (Seed & Wood 1971 and see 5.2[e]). Even the use of duplex systems to image the aorta in two planes from the suprasternal notch (as most recently suggested by Notterman et al 1989) may not improve accuracy, since there may be poor coaxial alignment in the elevational plane, leading to underestimation of the blood flow velocity (Wilson et al 1987).

Coronary flow is not included in Doppler assessment of cardiac output by this method and since the Doppler method determines ascending aortic flow, if a patent ductus arteriosus is present the measured flow will reflect the left to right shunt through the ductus in addition to systemic flow. Thus changes in aortic root flow may merely reflect changes in ductal flow rather than true changes in cardiac output.

"Absolute" aortic flow measurements require accurate vessel diameter measurement, as this figure is squared for CSA calculation and appears to be the major source of error with this technique (Fisher et al 1983). This may be more accurately measured with M-mode echocardiography, and cardiac output recorded in this way correlates well with standard thermodilution studies (Lang-Jensen et al 1983). Other workers have obtained better correlation by calculating aortic diameters from angiograms performed during catheterisation (Goldberg et al 1982). The "correct" site at which to measure aortic diameter is uncertain; indeed the aortic CSA is not perfectly circular and may vary in size during the cardiac cycle (Bernstein 1987). Other factors affecting aortic root diameter are the output state of the heart and the presence of congenital heart disease (Scholler et al 1986). An alternative Doppler technique to provide volumetric blood flow measurement without the need to measure vessel size or angle of insonation has been proposed (Hottinger & Meindl 1979, Evans JM et al 1986). A wide ultrasonic beam

positioned at the suprasternal notch is used to obtain a Doppler spectrum corresponding to all the flowing blood and simultaneously the ultrasonic power obtained with a narrow reference beam placed within the lumen compensates for the attenuation in the overlying tissues. This method has to date not gained widespread clinical acceptance.

An alternative approach is to consider the cardiac output as the distance moved by a volume of blood by the ventricular stroke (Haites et al 1984). The rationale for this approach is that to convert "stroke distance" to volumetric flow requires calculation of aortic CSA. This in turn is indirectly related to body surface area and both reflect body size (big people have big aortas). Having measured stroke distance directly, it seems unnecessary to convert it to volumetric flow using CSA, only to correct for body size by dividing by surface area (which in any case is not applicable to neonates). Thus if stroke distance is biologically corrected for body size, it should be independent of body surface area (demonstrated by Mowat et al 1983) and the aortic blood velocity might be expected to have a similar value throughout childhood (Light 1978). To be of value, stroke distance should be proportional to stroke volume, and this has been confirmed (Ihlen et al 1987).

Another important factor which could potentially affect blood velocity in the aortic root is blood pressure. Considering normal variability, aortic blood flow velocity appears independent of blood pressure (Mowat et al 1983), but the ability of Doppler techniques to detect a change in cardiac output is slightly reduced if there is a large accompanying fall in blood pressure (McLennan et al 1986). The latter study also demonstrated good correlation between absolute flow changes and blood velocity changes in the aorta both in vitro and in vivo.

Bernstein (1987) reviewed the use of Doppler assessment of cardiac output. Since there is no current unanimity of opinion regarding (a) which echocardiographic

method or convention should be employed for aortic "diameter" measurements, (b) which site(s) are most suitable for cross sectional area measurements and velocity analyses (c) which type of Doppler to use and (d) whether to use the mean or peak Doppler shift for integration of the velocity profile, the use of such techniques has limitations in terms of "absolute" measurements. This holds true even before making comparisons with "gold standard" techniques (Schuster & Nanda 1984). However, the technique has been shown to be extremely reproducible (Chandraratna et al 1984) and might therefore be used for monitoring intra-individual changes.

8.1b(iii) Other Methods

Non-invasive measurement of factors related to cardiac output such as ventricular volume using two-plane cineangiography and ejection fraction (the difference between ventricular volumes at the end of diastole and the end of systole) using radionuclide labelling do not lend themselves to repeated determinations of output. In addition they cannot be used accurately to assess actual cardiac output.

8.1(c) Thermodilution versus Doppler (2).

Hypothesis: The reproducibility of Doppler assessment of cardiac output compares favourably with that obtained using thermodilution.

(i) Introduction

Clearly many factors can influence the determination of cardiac output, whatever method is used. It therefore seemed essential to perform an independent comparison of the Doppler technique against thermodilution in an infant population to determine its reproducibility, prior to attempting its use in a neonatal setting.

8.1c(ii) Patients

The study group comprised 10 infants (age range 1-11 months, mean 4.4

months) undergoing cardiac catheterisation as part of their management for congenital cardiac disease. All had either (a) normal cardiac anatomy (post surgery) or (b) a septal defect. Full clinical details are given in table 8.1.

8.1c(iii) Study Procedure

All catheter studies were performed using intramuscular Pethidine Compound (0.1 $ml.kg^{-1}$) for sedation. A 5F thermodilution catheter (Spectramed SP5105H) was inserted percutaneousiy under local anaesthesia into one femoral vein and positioned either in the pulmonary artery (if cardiac anatomy was normal) or manipulated into the aortic root (if a septal defect was present). The position of the catheter was confirmed radiographically. Three thermodilution cardiac outputs using 5ml of chilled dextrose 5% solution were performed in each patient at 2 minute intervals, using a Gouid SP1435 Cardiac Index Computer. The system incorporates an in-line temperature probe to ensure suitable injectate temperatures.

Immediately following each thermodiiution measurement, a Doppler estimation of stroke distance was performed, the probe being removed between each determination. The ascending aorta was visualised from the suprasternal notch, using the same ATL 600 duplex Doppler system as described in 5.3[a]. The Doppler sample volume was set at 5mm and positioned in the centre of the aortic root, care being taken to minimise the angle of insonation. High filter and Doppler power settings were as described in 5.3[a]. Once the optimum waveform had been obtained, signals were recorded onto digital audiotape and analysed as described previously (5.3[a]). The maximum velocity over the cycle was used to calculate stroke distance, since for the purposes of analysis a "plug" aortic velocity profile was assumed. Any error introduced by the fact that the flow profile is probably somewhere between plug-like and parabolic, thus altering the relationship between maximum and mean velocity (see 5.2[e]) would not affect assessment of reproducibility of

Infant	Diagnosis	Age (months)	Aortic CSA (cm^2)	Minute Distance (m)	Cardiac Output ($l.min^{-1}$) Doppler	$\bar{D}$	Thermodilution	$\bar{T}$	Mean $\bar{D}$, $\bar{T}$	Difference $\bar{D} - \bar{T}$	Paired Estimations (Doppler) Mean	Paired Estimations (Doppler) Difference	Paired Estimations (Thermodilution) Mean	Paired Estimations (Thermodilution) Difference
1	VSD	4	1.13	19.8 18.2 16.8	2.24 2.05 1.90	2.06	1.17 1.13 1.04	1.11	1.59	0.95	2.15	0.19	1.19	0.04
2	ASD	3	1.13	16.3 16.2 17.3	1.84 1.83 1.95	1.87	1.40 1.32 1.36	1.36	1.62	0.51	1.84	0.01	1.36	0.08
3	Arterial Switch for simple TGA	11	1.33	18.8 18.7 17.7	2.50 2.49 2.35	2.45	1.71 1.81 1.80	1.77	2.11	0.68	2.50	0.01	1.76	-0.10
4	VSD	3	1.54	13.3 10.0 10.5	1.74 1.54 1.62	1.63	1.73 1.54 1.69	1.65	1.64	-0.02	1.64	0.20	1.63	0.19
5	VSD ? Coarctation	3	2.27	4.1 9.4 6.1 7.0	0.93 2.13 1.38 1.59	1.51	1.19 2.39 1.88 2.20	1.92	1.72	-0.41	1.53	-1.20	1.79	-1.20
6	Arterial Switch for simple TGA	1	1.33	7.8 7.6 8.0	1.04 1.01 1.06	1.04	0.90 0.88 0.93	0.90	0.97	0.14	1.03	0.03	0.89	-0.02
7	Repaired Coarctation (normal intra-cardiac anatomy)	4	1.13	15.4 15.6 17.0	1.74 1.76 1.92	1.81	1.52 1.63 1.82	1.66	1.74	0.15	1.75	-0.02	1.57	-0.11
8	Arterial Switch for simple TGA	2	1.33	9.2 10.5 8.0	1.22 1.40 1.06	1.23	1.29 1.25 1.24	1.26	1.25	-0.03	1.31	-0.18	1.27	0.04
9	Patent Foramen Ovale	6	1.13	16.2 15.7 15.6	1.83 1.77 1.76	1.79	1.95 1.76 1.79	1.83	1.81	-0.04	1.80	0.06	1.86	0.19
10	VSD	7	1.33	19.4 20.5 16.8	2.58 2.73 2.23	2.51	2.41 2.77 2.72	2.65	2.58	-0.14	2.66	-0.15	2.59	-0.36

Table 8.1

Patient and study details for Doppler/thermodilution validation. $\bar{D}$ & $\bar{T}$ refer to mean of replicate readings in each infant for Doppler & thermodilution respectively.

Paired estimations refer to the first pair of values in each set of replicate measurements.

the technique. Aortic diameter measurements for CSA estimations were made from reai-time ultrasound images. Cardiac output was caicuiated as the product of stroke distance and aortic CSA, the latter being assumed to be circular. This assumption wouid also not affect reproducibility.

8.1c(iv) Statistical Analysis

Initiaiiy a direct comparison between cardiac output obtained from the two methods was attempted. A mean output in each infant was calculated for both the Doppler and thermodiiution estimations. The mean of these two values for each infant was plotted against the difference between them (table 8.1 & figure 8.1). The mean difference in output estimated by the two methods was 0.18 $l.min^{-1}$, (SD 0.39 $l.min^{-1}$), which clearly shows a wide range with poor correlation.

The aim of the study however was to assess the reproducibility of the two techniques, and this question was addressed using the method of Bland and Altman (1986). The first pair of estimates of cardiac output were taken for each method in each infant. The difference between the two estimations was plotted against their mean (table 8.1 & figure 8.2). One infant with a VSD demonstrated very poor reproducibility for both methods (possibly related to activity and changes in the degree of intracardiac shunting during the procedure) and was therefore excluded from subsequent analysis. The remaining infants showed no significant differences in reproducibility, the standard deviation of the differences being 0.129 $l.min^{-1}$ for Doppler and 0.171 $l.min^{-1}$ for thermodilution. Thus despite the poor correlation of the two methods, the reproducibility of both methods was good, Doppier performing at least as well as thermodiiution. It was therefore felt appropriate to apply the technique to estimating changes in stroke distance in ventiiated preterm infants.

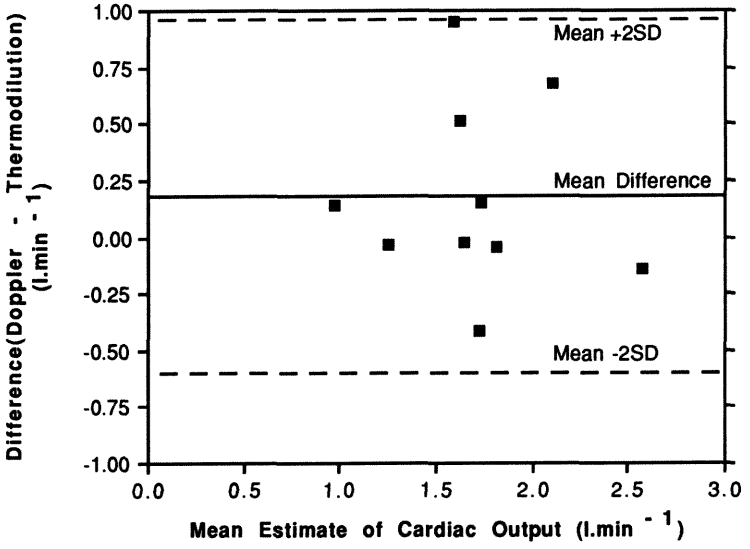

Figure 8.1

Poor correlation of Doppler and thermodilution estimations of cardiac output. See text for details.

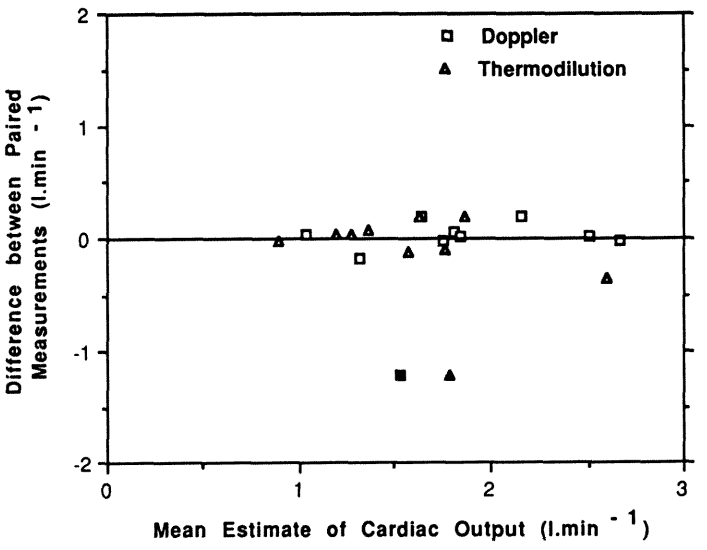

Figure 8.2

Both Doppler (□) and thermodilution (Δ) showed good reproducibility. One infant with a VSD (shaded symbols) showed poor reproducibility for both methods, possibly due to changes in shunting or to activity during the procedure.

8.2 Cardiac Effects of CO_2 in Ventilated Preterm Neonates

Hypothesis: The rise in blood pressure in ventilated preterm infants following a rise in $PaCO_2$ results from an increase in cardiac output.

(a) Patients and Methods

Patient eligibility criteria were as described in section 7.2 and in addition infants with a pneumothorax were excluded, in view of potential compromise of cardiac function. The study procedure was identical to that in section 7.3 with regard to recording of ventilatory and blood pressure parameters and arterial blood gases, but instead of CBFV recordings, Doppler estimations of aortic stroke distance were made. The ascending aorta was visualised via the suprasternal notch, using an identical Doppler system to that in 5.4[b]. A second set of baseline recordings were made after an interval of 10 minutes to ascertain the baseline variability, before the placement of a dead-space into the ventilator circuit as described previously (see 7.3[b]). Following a period of equilibration (10-12 minutes), repeat determinations of MABP, ABG and stroke distance were made.

8.2(b) Statistical Analysis

As a normal distribution of the data could not be assumed, Wilcoxon's signed rank test was used to look for differences in blood pressure, heart rate and stroke distance before and after the rise in $PaCO_2$. The effect on these differences of gestational and postnatal age and whether the infant was paralysed with pancuronium was also examined using the Mann-Whitney test for unpaired data in view of the previous findings (see 7.5[c] & [d]). For the purposes of the latter analyses the effect of gestational age was examined by dividing the infants into those ≤30 weeks (n=11) and those ≥31 weeks. The effect of postnatal age was examined by dividing the infants into those studied ≤24 hours of age (n=9), and those studied ≥25 hours.

8.2(c) Results

Twenty one infants (gestational age 24-34 weeks, mean 30 weeks) were studied on a total of 45 occasions, 12 infants being studied at least twice (see Appendix 4). Postnatal age at the time of study ranged from 5 to 115 hours (mean 38 hours). There was no significant difference between the two baseline values of heart rate (p=0.59), stroke distance (p=0.44), minute distance (p=0.20) or blood pressure (p=0.85). Mean baseline values were as follows: $PaCO_2$ 4.7 kPa (range 3.52-6.68 kPa); MABP 41 mm Hg (range 30-57 mm Hg); heart rate 147 beats.mln^{-1} (range 121-176).

The mean rise in $PaCO_2$ induced was 1.02 kPa (SEM 0.07 kPa), which resulted in a significant rise in MABP (p=0.006). The mean rise in MABP corrected for a 1 kPa rise in $PaCO_2$ was 3.7 mm Hg (SEM 1.1 mm Hg), which represented a mean rise of 8% from baseline values. This rise was unaffected by gestation (p=0.5), the use of paralysing agents (p=0.28) or postnatal age (p=0.46). However, for the group as a whole the change in heart rate was not significant (p=0.16) and a fall in both stroke and minute distance occurred (p=0.023 and 0.02 respectively). The changes in minute distance are shown in figure 8.3, and it can be seen that the response was heterogeneous, with 6 infants demonstrating a rise in minute distance. Four of these 6 infants were therapeutically paralysed with pancuronium and had more severe respiratory disease at the time of study, but clearly this subgroup is too small to draw further conclusions. For the group as a whole, the mean fall in minute distance for a 1 kPa rise in $PaCO_2$, 1.59 m (SEM 0.63 m), represented a 10% change from baseline values and was also unaffected by gestation (p=0.70), the use of paralysing agents (p=0.21) or postnatal age (p=0.41).

A rise in PaO_2 (mean 0.26 kPa, SEM 0.53 kPa) occurred in these infants but did not attain statistical significance for the group as a whole (p=0.64).

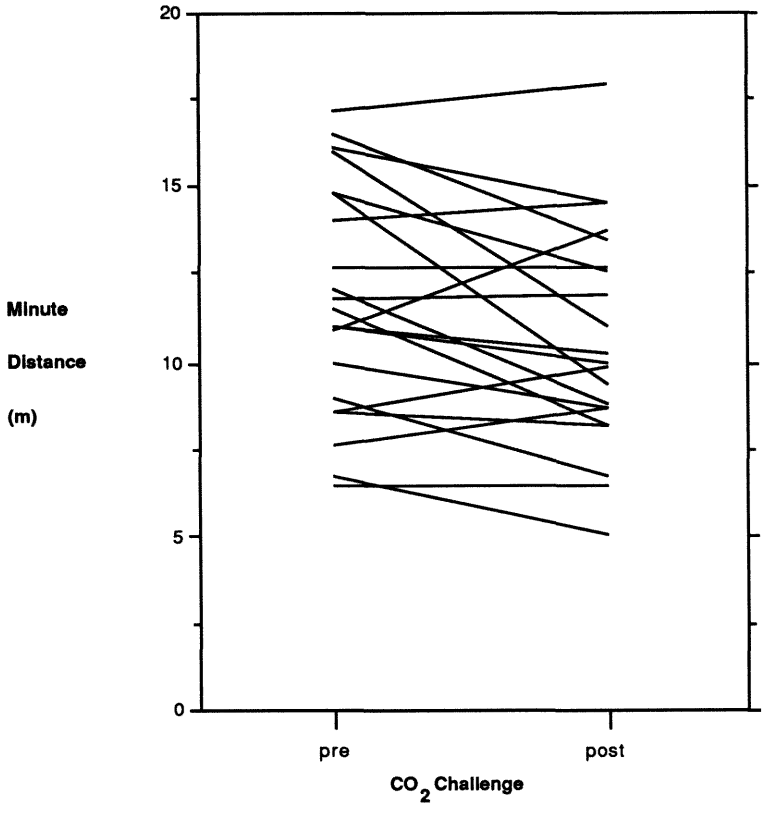

Figure 8.3

Effects of a 1 kPa rise in $PaCO_2$ on minute distance in ventilated preterm infants.

8.2(d) Discussion

The finding that in response to the rise in $PaCO_2$ blood pressure rose despite no change in heart rate, combined with a fall in stroke volume was unexpected. The quantitative fall in stroke volume for the study group as a whole may not be of clinical significance (see 8.1b[i]), but of more importance is the fact that a rise did not occur. Archer et al (1986) also reported no change in heart rate following a rise in $PaCO_2$ in term infants, but blood pressure was not recorded in that study. Whilst CO_2 is known to have a depressant action on isolated or beta-blocked heart preparations, reducing both rate and force of contraction, in the presence of intact autonomic innervation the sympathetic response to the rise in $PaCO_2$ results in a net increase in cardiac output (see 3.3b[III]). These findings suggest that the observed increase in blood pressure in this situation depends on an increase in peripheral resistance. Rennie (1989) observed that infusions of either colloid or inotrope (dopamine) produced a fall in variability of CBFV. It was postulated that this fall resulted from correction of a degree of hypovolaemia and the finding that the same effect occured with dopamine alone as with colloid suggests that part of its effect is mediated by changes in peripheral vascular resistance.

Cullen and Eger (1974) demonstrated a 7% rise in blood presure per 1 kPa rise in $PaCO_2$ in healthy adults, but in contrast heart rate and stroke volume rose by 21% and 8% respectively and peripheral resistance (measured in the limb) fell by 13%. The vasodilatory effects of rises in $PaCO_2$ on limb and splanchnic vascular beds are well documented in animal studies (see 3.3b[iv]), there being a more marked response in the absence of autonomic innervation or with the use of sympathetic blockade. The reasons for the difference between the preterm and the adult response are not clear. It may reflect incomplete maturation of autonomic innervation of the heart in the former, thus giving more importance to factors such as vascular innervation and circulating catecholamines.

The basal blood flow to the brain in the neonate is proportionately greater than in the adult and, as in the adult, a fall in cerebrovascular resistance accompanies a rise in $PaCO_2$ (see chapter 7). This means that for total peripheral resistance to increase there must be a considerable increase in peripheral resistance in other areas of the circulation.

The possible dependence of blood pressure on components of peripheral resistance may also help explain the rise in PaO_2 which accompanied the rise in $PaCO_2$ in this and the ventilator rate study (see 6.4[f]). A rise in blood pressure secondary to alterations in peripheral (systemic) resistance would be more likely to affect atrial shunting (presumably by an effect on left ventricular end diastolic pressure) than if it were due simply to changes in cardiac output alone, since the latter would probably not affect the degree of shunting. The overall non-significant change in PaO_2 in this group may have been due to factors such as the relatively small number of studies, postnatal age and general condition of the infants.

Previous studies have examined the effects of stroke volume and peripheral resistance on cardiac output in newborn animals and humans under several conditions. Romero and Friedman (1979) sugggested that the cardiovascular response to a volume load in newborn sheep was impaired both due to the inability to alter peripheral resistance acutely and because of limited preload reserve related to reduced left ventricular compliance. Clyman et al (1987) studied the effects of graded occlusion of the ductus arteriosus in sheep and demonstrated changes in stroke volume rather than rate, suggesting that when afterload is low stroke volume is a major determinant of cardiac output. Similar results were obtained in a small group of term infants (Lundell et al 1988). The infants studied here were ventilated and this may to some extent have affected both pre- and afterload (see 6.2 & 6.3), thus affecting the response to the rise in $PaCO_2$.

Summary

Doppler ultrasound appears to provide a simple means of non-invasive assessment of changes in cardiac output in infants. The neonatal data suggest that ventilated preterm infants show a different cardiovascular response to changes in $PaCO_2$ to that in the adult.

Chapter 9

Conclusion

The data presented here are significant in several areas. Firstly, they have provided further information on the cerebrovascular regulatory mechanisms in the sick preterm infant. The finding of apparent gestational and postnatal age differences in factors influencing the CO_2 response is important, though the reasons for these differences remain unclear. Certainly the role of neural and humoral regulatory mechanisms in the preterm setting warrant further study. It may be that certain infants are stressed beyond the compensatory limits of such mechanisms and are therefore at risk of impaired cerebral perfusion and brain injury. Hypotension remains the most likely final common pathway in the genesis of such injury, despite a lack of evidence linking it directly with PVL. Clearly the demonstration that "pressure-passivity" of CBF does appear to occur under certain conditions adds support to the Pape and Wigglesworth model for the development of PVL.

Secondly, in view of the wide range of ventilatory support that the infants studied were receiving it was important to consider the potential adverse circulatory effects of ventilation, though the inability to perform compliance measurements on all infants to some extent limits the comparability of the results. Previous work on the effects of PEEP suggested that any circulatory effects of changes in ventilatory parameters (at least within the currently used ranges) were negligible in comparison with those arising as a result of changes in $PaCO_2$ and the unexpected findings relating to the use of fast ventilator rates certainly warrant further study to determine (a) their clinical importance and (b) whether similar changes occur in unparalysed infants.

Thirdly, the possibility that pancuronium may predispose to pressure passive cerebral blood flow has important clinical implications for the future use of this drug in neonatal intensive care. Previous studies have claimed beneficial effects from its use both in terms of IVH and in terms of prevention of pneumothorax, the latter clearly having secondary effects on blood pressure. The potential risk demonstrated here may be only of clinical significance in the unstable infant who thus has other known risk factors associated with PVL. It might be argued that infants requiring paralysis represented the most severely sick of the cohort and as a consequence had impaired cerebrovascular regulation. However it could be argued equally that such infants had to be paralysed because they were too vigorous and were thus interracting with the ventilator In a disruptive manner. A possible next step would be to compare the effects of other agents that have pharmacologically "purer" actions with pancuronium.

The on-line Doppler/blood pressure recording system enabled the cerebral haemodynamic effects of therapeutic manoeuvres (ventilatory or pharmacological) to be observed over prolonged periods of time without undue handling of the infant. These studies have not established a clinical use for Doppler in terms of cerebral haemodynamic monitoring, but again within the limitations of the technique this method may be used to provide information on changes within the cerebral circulation under more "normal" conditions. Areas of particular interest would be the effects of manoeuvres which influence blood pressure such as transfusion or the use of inotropic agents, especially in those groups of infants identified in these studies in whom blood pressure passive CBF has been suggested to occur. It would be of interest to study any changes in blood pressure resulting from such manoeuvres in relation to the cardiac parameters of heart rate and stroke distance and the reproducibility of Doppler assessment of the latter demonstrated may therefore be of clinical use.

In summary carbon dioxide has profound effects on all components of the cardiovascular system in adults and these studies indicate that its overall effect in the ventilated preterm neonate is similar, although certain factors may affect the response to changes in $PaCO_2$. The initial aim of the foregoing work was simply to assess whether the nature or degree of change in CBFV in response to a rise in $PaCO_2$ in a series of ventilated preterm infants would predict subsequent PVL, and in retrospect this may have been too simplistic an approach. Cerebral blood flow is an extremely complex variable under resting conditions alone and the use of Doppler ultrasound to monitor changes in blood flow velocity in one cerebral artery resulting from a "physiological" stimulus which has profound widespread effects and relate that change to a complex pathophysiological process is far from an "ideal" scientific study. it might be expected that stable infants (a condition for study) would have a "stable" CO_2 response and clearly it would have been inappropriate to stress acutely unstable infants. in addition, linking the applied stimulus (the rise in $PaCO_2$) and observed changes may have been several interrelated processes, for example involving neural and humoral pathways which have not been examined by this work.

However in research of this nature the safety of the infants studied is paramount. The techniques used have been validated under more "ideal" experimental conditions and also within the framework of the questions being addressed by these studies. Within these limitations the methods used would appear valid, simple to apply and without apparent ill-effect. They have yielded potentially important results and suggested further areas of study in this field.

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Appendix 1

Raw Data for Chapter 5

(On-line Doppler system)

Time (min)	CBFV ($cm.s^{-1}$)	Blood Pressure (mm Hg) Systolic	Mean	Diastolic	R.A.P./10^4 ($kg.m^{-2}.s^{-1}$)	Time (min)	CBFV ($cm.s^{-1}$)	Blood Pressure (mm Hg) Systolic	Mean	Diastolic	R.A.P./10^4 ($kg.m^{-2}.s^{-1}$)
5	5.1	57.4	48.7	40.6	12.70	135	5.0	55.6	46.3	38.0	12.36
10	4.2	58.0	48.2	39.5	15.21	140	4.3	56.9	47.3	38.6	14.50
15	-	65.0	53.5	43.5	-	145	5.1	56.4	46.8	38.3	12.28
20	5.7	70.5	56.8	45.5	13.34	150	6.4	63.5	53.0	43.7	11.03
25	4.4	61.5	50.7	41.2	15.23	155	5.3	54.7	45.3	36.7	11.46
30	5.0	59.6	49.2	40.0	13.05	160	5.1	61.2	49.5	39.4	12.98
35	4.6	72.7	59.2	47.8	17.21	165	4.9	59.3	49.7	40.9	13.58
40	5.2	67.7	56.3	46.2	14.47	170	6.5	56.8	47.8	39.5	9.87
45	5.0	61.9	50.6	40.7	13.41	175	5.4	55.8	45.9	37.2	11.33
50	6.2	64.9	54.4	45.0	11.71	180	4.4	52.6	43.4	35.2	13.21
55	5.3	70.0	57.3	46.1	14.37	185	6.7	60.5	50.0	40.9	9.98
60	5.7	66.0	54.2	44.0	12.81	190	5.7	60.8	51.2	42.4	12.06
65	5.1	67.2	54.1	43.3	14.13	195	5.6	63.8	51.8	41.6	12.33
70	4.8	65.2	52.9	42.7	14.61	200	6.2	63.9	53.2	43.6	11.38
75	6.1	72.7	59.1	47.5	12.95	205	6.0	66.0	54.5	44.4	12.22
80	8.1	69.4	56.0	44.8	9.29	210	7.8	64.4	52.3	42.0	8.98
85	6.0	66.8	55.1	45.1	12.22	215	-	69.4	57.9	47.7	-
90	5.2	60.6	49.3	39.4	12.76	220	-	61.1	50.8	41.8	-
95	4.2	55.6	45.5	36.7	14.61	225	6.7	65.1	52.7	42.4	10.52
100	5.9	70.6	59.6	49.8	13.45	230	7.2	61.9	51.2	41.5	9.43
105	5.3	28.7	22.9	17.8	5.79	235	8.7	65.6	54.2	44.1	8.30
110	5.2	61.7	51.5	42.5	13.13	240	9.0	61.2	50.2	40.5	7.44
115	5.1	58.2	48.4	39.6	12.77	245	-	61.0	50.7	41.6	-
120	6.1	64.0	53.8	44.9	11.71	250	5.6	57.6	46.9	37.4	11.23
125	5.0	62.8	51.5	41.6	13.72	255	6.4	59.2	48.5	39.0	10.04
130	5.3	64.3	52.8	42.9	13.32						

Data for figure 5.3.

Time (min)	CBFV ($cm.s^{-1}$)	Blood Pressure (mm Hg) Systolic	Mean	Diastolic	R.A.P./10^4 ($kg.m^{-2}.s^{-1}$)
5	4.7	36.6	28.6	22.5	8.09
10	3.1	33.9	27.0	21.3	11.43
15	4.9	33.4	26.3	20.6	7.21
20	3.3	30.4	24.0	18.7	9.84
25	5.4	38.0	29.2	22.8	7.22
30	5.0	31.6	25.3	20.0	6.76
35	4.2	34.1	28.2	23.1	8.86
40	4.1	35.7	30.6	25.9	10.02
45	5.6	37.3	31.3	26.3	7.45
50	6.9	35.9	29.0	23.5	5.60
55	8	35.7	28.6	23.2	4.75
60	8.8	35.7	27.9	21.9	4.25
65	10.2	36.5	29.1	23.6	3.80
70	9.2	31.0	26.0	21.4	3.77
75	6.6	31.2	26.2	21.6	5.30
80	5.6	37.7	31.4	26.9	7.52
85	4.5	30.3	24.5	19.4	7.21
90	3.7	30.4	24.8	19.8	8.81
95	5.3	36.8	28.7	22.7	7.19
100	4.6	30.5	24.2	19.0	7.07
105	4.7	29.2	23.7	18.9	6.78
110	4.1	37.7	29.6	23.3	9.75
115	2.3	33.7	27.9	22.9	16.04
120	3.2	33.6	28.7	24.6	11.82
125	4.4	33.5	28.2	23.5	8.54
130	2.4	30.1	24.3	19.3	13.37
135	3.3	26.7	23.4	19.9	9.57
140	2.3	29.4	26.5	23.0	15.63
145	4.1	34.0	28.2	23.0	9.25
150	2.8	30.6	24.9	19.9	11.97
155	3.9	36.7	29.5	23.7	10.19
160	5.8	36.5	30.8	26.1	7.06
165	7.9	37.6	28.6	22.1	4.83
170	6	28.4	22.6	17.6	5.00
175	5.1	37.5	30.9	25.5	8.08

Data for figure 5.4.

Time (min)	CBFV ($cm.s^{-1}$)	Blood Pressure (mm Hg) Systolic	Mean	Diastolic	R.A.P./10^4 ($kg.m^{-2}s^{-1}$)
5	6.0	43.6	33.6	24.5	7.44
10	6.2	39.7	29.6	20.8	6.43
15	4.7	36.7	26.3	17.8	7.50
20	8.0	39.6	29.3	20.0	4.91
25	9.1	38.1	27.1	17.8	3.98
30	9.2	42.7	31.6	21.8	4.58
35	6.7	35.3	25.1	16.9	5.04
40	4.7	36.8	26.4	18.6	7.50
45	6.0	37.2	27.1	18.3	6.05
50	5.5	34.1	24.1	16.0	5.82
55	5.6	33.9	23.4	15.6	5.53
60	6.0	50.3	38.4	29.3	8.57
65	12.6	51.6	37.5	26.3	3.95
70	3.8	50.2	37	26.1	12.96
75	5.5	50.2	36.8	26.0	8.94
80	4.3	48.8	35.3	24.1	11.05
85	3.6	45.2	32.5	22.6	12.16
90	3.9	42.9	29.9	21.1	10.3
95	3.3	39.2	27.4	19.7	11.11
100	2.4	36.5	26	18.8	14.27
105	4.9	49.6	36.5	26.1	10.05
110	4.4	48.7	36.3	26.4	10.96
115	4.1	44.7	33.1	23.3	10.75
120	4.8	47.0	35.1	26.1	9.73
125	2.9	39.2	28.9	21.1	13.22
130	2.9	44.1	32.3	23.2	14.73
135	2.6	37.1	25.6	17.3	13.18
140	3.3	38.2	26.1	17.5	10.39
145	4.6	43.3	31.0	21.2	9.01
150	4.3	43.8	31.7	21.7	9.81
155	3.4	38.1	29.5	22.3	11.69
160	2.7	36.4	23.8	15.7	11.98
165	6.7	52.4	37.5	26.1	7.43
170	4.2	41.2	28.0	17.5	8.99
175	4.7	40.4	27.4	17.7	7.72
180	5.5	46.9	32.0	21.3	7.82
185	3.8	40.2	26.8	17.2	9.40
190	5.1	50.9	35.7	24.5	9.33
195	4.8	33.3	20.7	12.5	5.80
200	2.9	33.5	20.1	11.5	9.30
205	2.7	31.4	19.3	11.6	9.42
210	3.4	29.7	18.1	11.0	7.11
215	5.6	44.7	29.1	17.9	6.95

Data for figure 5.5.

Appendix 2

Raw Data for Chapter 6

Changes in $PaCO_2$, PaO_2, CBFV, MABP and minute ventilation with increasing ventilator rate (30-40, 50-60 & 100 breaths per minute). A further set of measurements were made at 100/minute with the pneumotachograph bias flow turned off, creating a dead-space effect (100 DS).

Infant	$PaCO_2$ (kPa) at each ventilator rate 30-40	50-60	100	100 (DS)
1	6.3	5.7	5.0	5.5
2	5.7	4.2	4.7	5.3
3	4.7	5.0	5.1	5.8
4	5.8	5.2	5.8	6.0
5	7.4	6.6	6.5	7.2
6	5.8	6.3	7.0	-
7	6.6	5.9	5.2	6.1
8	7.7	7.2	6.3	7.1
9	6.8	6.2	5.9	4.6
10	6.1	5.6	5.6	5.8
11	6.2	6.4	6.3	6.7
12	6.1	6.2	6.8	-
13	6.4	6.1	6.0	-
14	5.3	4.9	4.8	5.0
15	-	7.0	6.7	-
16	6.2	5.8	5.9	6.4
17	5.8	4.6	5.6	6.2
18	7.2	6.5	6.9	6.9
19	4.2	3.0	3.2	4.2
20	7.0	6.3	6.5	6.9

Infant	PaO_2 (kPa) at each ventilator rate 30-40	50-60	100	100 (DS)
1	11.6	10.8	11.0	11.2
2	7.0	10.1	8.6	7.6
3	8.1	8.9	8.0	7.8
4	7.3	7.2	7.2	9.7
5	17.8	16.1	16.9	20.4
6	9.6	9.9	8.3	9.0
7	15.2	13.1	11.6	13.4
8	8.6	9.3	9.6	9.2
9	7.6	6.9	6.3	6.8
10	7.7	7.2	6.7	7.6
11	9.7	8.4	8.7	8.6
12	7.2	6.8	7.1	-
13	12.3	8.1	10.9	-
14	8.4	7.9	7.3	7.7
15	-	6.9	5.4	-
16	7.9	8.1	7.4	7.8
17	6.1	7.5	6.6	5.9
18	10.6	10.9	10.4	10.9
19	8.1	8.5	8.0	7.9
20	11.7	11.2	10.9	-

	CBFV (cm.s-1) at each ventilator rate			
Infant	30-40	50-60	100	100 (DS)
1	6.5	4.5	3.0	3.5
2	7.0	6.0	6.5	6.5
3	8.5	10.0	8.5	10.5
4	8.0	6.0	6.5	11.0
5	10.0	6.5	6.5	11.0
6	6.5	5.0	6.5	-
7	5.2	4.8	2.8	4.1
8	6.8	5.7	5.5	6.3
9	7.8	5.5	5.5	4.6
10	7.5	5.9	5.8	5.9
11	5.0	4.9	4.4	4.6
12	7.1	7.5	8.5	-
13	3.7	2.5	1.8	1.9
14	3.7	3.7	2.9	4.2
15	-	4.9	5.9	-
16	3.8	4.3	3.9	5.0
17	4.9	4.0	5.7	6.2
18	12.2	8.5	8.5	9.7
19	3.4	2.2	2.2	2.1
20	7.0	6.0	6.5	6.5

	MABP (mm Hg) at each ventilator rate			
Infant	30-40	50-60	100	100 (DS)
1	42	39	40	43
2	50	60	56	54
3	51	50	52	53
4	39	38	34	42
5	50	47	44	48
6	44	45	50	-
7	54	54	36	38
8	36	31	33	37
9	51	44	44	46
10	45	48	43	45
11	55	54	47	50
12	45	41	44	-
13	38	44	37	38
14	-	-	-	-
15	-	35	39	-
16	-	-	-	-
17	42	40	40	41
18	56	49	50	52
19	36	34	35	36
20	55	54	55	60

Infant	Minute Ventilation (ml) at each ventilator rate 30-40	50-60	100	100 (DS)
1	400	530	621	659
2	570	858	1170	1210
3	636	804	1180	1180
4	546	725	1180	1140
5	-	565	910	910
6	521	594	767	-
7	544	720	1000	1000
8	477	618	903	870
9	1200	1440	1440	1440
10	450	516	890	890
11	450	750	1125	1060
12	405	600	590	590
13	384	492	680	680
14	438	702	970	910
15	-	336	500	500
16	504	690	1030	1000
17	375	486	625	625
18	214	300	360	320
19	864	1256	1440	1440
20	680	900	1400	1400

Appendix 3

Raw Data for Chapter 7

1) Data for calculation of resistance of dead spaces used to increase $PaCO_2$ (figure 7.2).

2) Details of Individual Infants in CO_2 Reactivity Studies.

Heading for each infant (e.g. **22/29/1.22/M/S/fl/pvl/pda**) gives study number, gestation (weeks), weight (kg), sex, outcome [survived (S), died (D)], cranial ultrasound appearances [flare (fl), PVL] and presence of patent ductus arteriosus (pda).

E.T.T.			E.T.T. + Dead Space		
Flow ($l.s^{-1}$)	Pressure ($cm\ H_2O$)	Resistance ($cm\ H_2O.l^{-1}.s$)	Flow ($l.s^{-1}$)	Pressure ($cm\ H_2O$)	Resistance ($cm\ H_2O.l^{-1}.s$)
0.125	3.68	29.40	0.123	3.71	30.15
0.097	2.32	23.92	0.102	2.64	25.88
0.082	1.74	21.22	0.088	2.00	22.73
0.070	1.35	19.29	0.073	1.48	20.27
0.058	0.97	16.72	0.060	1.00	16.67
0.050	0.81	16.1	0.052	0.81	15.50
0.040	0.61	15.25	0.040	0.48	12.00

Resistance of endotracheal tube with & without dead space (inspiratory phase).

E.T.T.			E.T.T. + Dead Space		
Flow ($l.s^{-1}$)	Pressure ($cm\ H_2O$)	Resistance ($cm\ H_2O.l^{-1}.s$)	Flow ($l.s^{-1}$)	Pressure ($cm\ H_2O$)	Resistance ($cm\ H_2O.l^{-1}.s$)
0.123	6.97	56.63	0.125	6.06	48.50
0.107	5.13	47.92	0.107	4.58	42.80
0.095	4.22	44.47	0.082	2.32	28.32
0.082	3.52	42.87	0.070	1.61	23.04
0.068	2.39	35.10	0.062	1.26	20.29
0.060	1.81	30.10	0.038	0.65	16.97
0.040	0.71	17.74			

Resistance of endotracheal tube with & without dead space (expiratory phase).

1/25/0.70/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.30	n	0.84	3/4	11.2/9.1	45/41	29.3/34.1	4.4/5.0	7.3/6.8	152/154

2/25/0.75/F/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
2.30	n	0.77	2/3	16.1/15.2	45/41	22.5/27.9	7.4/7.8	10.2/12.8	154/153
12.16	n	1.54	2/7	12.1/9.0	48/46	39.8/42.0	5.0/5.4	6.7/5.0	136/138
40.46	n	0.37	6/5	2.8/6.1	43/52	42.0/37.1	1.7/1.5	- / -	- / -

3/25/0.76/M/S/pvl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.15	n	0.76	1/1	12.5/14.2	32/35	39.7/40.4	2.2/5.1	14.0/12.3	122/136

4/26/0.99/M/D/pvl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
3.10	n	1.37	-	-	22/30	-	-	5.4/21.0	- / -
22.30	n	1.34	5/6.5	5.2/6.5	26/28	-	-	7.3/8.1	163/163

5/26/0.85/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
7.30	n	0.75	4/6	7.8/7.8	30/32	-	-	3.8/6.4	125/124
42.50	y	1.07	3/3.5	3.9/4.7	20/21	-	-	5.3/6.3	165/162

6/26/0.85/F/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
8.00	n	0.87	3/3.5	4.1/3.4	29/30	38.3/42.6	1.8/2.3	10.0/13.8	122/120
8.00	n	0.84	3.5/4.5	3.4/9.6	30/31	42.6/45.0	2.3/3.4	13.8/14.5	120/115

7/26/0.88/F/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
9.00	n	0.90	3/4.5	3.7/3.8	43/43	48.7/52.4	0.9/3.8	7.9/7.8	157/149
9.00	n	0.96	4.5/4	3.8/4.7	43/43	52.4/52.7	3.8/4.0	7.8/8.5	149/152
33.00	y	1.48	5/9	3.4/3.0	41/43	48.7/54.4	4.2/1.7	5.7/6.2	160/155
50.00	y	1.87	7/17	2.3/1.9	35/51	42.5/60.0	1.8/1.1	7.6/8.1	149/170

8/26/1.02/M/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
20.00	n	0.79	2/3.5	14.8/10.5	24/30	-	-	7.4/8.7	133/139
37.30	n	0.79	- / 4	-/10.0	40/40	-	-	7.3/8.3	-/147
110.00	n	0.46	7.5/7	3.6/3.5	28/39	-	-	12.1/13.0	156/152

9/26/1.15/M/S/fl/pvl/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.45	n	0.82	3.5/4	5.4/11.9	42/42	48.7/50.1	1.0/4.3	13.8/9.5	136/127
28.45	n	0.94	4.5/6.5	3.4/10.5	30/32	34.9/38.4	3.1/3.0	8.3/11.4	140/146
28.45	n	1.24	6.5/6.5	10.5/6.8	32/31	38.4/36.2	3.0/5.3	8.3/9.8	146/141
70.45	n	0.99	5.5/8	4.1/5.7	37/40	42.5/43.7	2.2/5.7	9.7/8.9	139/142

10/26/1.15/M/D/fl/pvl/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
7.00	n	1.62	2.5/3	11.1/18.1	34/32	39.8/36.8	2.1/6.7	8.3/10.9	140/145
26.30	n	1.24	3/3	10.7/31.6	30/34	-	-	9.8/8.1	146/146
54.30	y	0.60	4/7	7.7/5.3	28/29	38.9/35.8	3.7/3.5	8.6/9.6	161/166
72.30	y	1.78	4/9.5	4.8/5.4	34/30	40.5/35.4	3.3/2.1	8.9/10.7	144/151
102.00	y	1.26	3/5.5	5.2/3.4	33/34	39.4/38.9	3.1/1.9	9.1/7.6	126/127
123.00	y	2.02	3/2.5	9.4/35.4	33/30	41.6/35.3	4.0/5.7	7.9/10.1	122/139
147.00	n	1.10	4/5	8.6/12.7	32/34	41.2/41.2	4.8/5.4	10.4/11.3	137/142
168.00	n	1.01	4/6.5	8.4/10.4	37/37	32.2/44.0	4.1/6.0	9.9/9.7	143/148
216.00	n	3.05	5/12	8.4/5.1	26/40	38.7/56.9	5.5/4.8	11.6/8.4	151/152

11/26/0.84/F/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.30	n	0.72	4.5/5	3.1/4.8	38/42	44.0/49.1	1.2/6.0	6.6/7.4	147/144
25.35	n	1.10	4.5/5	14.0/11.1	31/30	36.0/37.3	8.7/10.0	11.6/8.3	152/142
50.00	n	1.75	5/11.5	3.9/6.3	29/34	32.2/40.2	5.5/6.2	10.1/7.5	160/158
98.30	n	0.79	6.5/6.5	8.9/8.3	33/28	39.7/33.0	3.2/5.0	10.8/14.6	142/151
176.30	n	0.65	6/6.5	4.8/8.1	32/38	37.0/43.0	2.5/4.8	10.7/11.9	147/142
194.00	n	1.17	5.5/8	7.5/10.2	32/41	37.5/47.2	4.1/4.0	9.9/8.5	154/147

12/27/0.92/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.50	n	0.77	3.5/5.5	10.5/4.9	32/35	38.3/40.4	1.8/2.0	7.4/10.1	145/145
19.50	n	0.18	4/8	4.0/5.7	35/39	44.0/51.3	2.7/2.0	6.1/4.2	130/137

13/27/1.15/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
7.30	n	0.87	5.5/5.5	4.0/6.4	34/43	41.7/45.8	1.9/3.1	10.3/16.7	127/128
21.30	n	0.97	4/9.5	10.5/10.4	36/40	43.7/46.6	4.6/6.2	9.1/5.1	158/161
46.30	n	1.37	5.5/8.5	7.0/7.2	36/40	43.6/49.7	2.5/1.4	5.3/4.7	154/148
66.30	y	1.44	4/11.5	6.0/3.1	43/54	46.7/61.4	2.7/2.2	5.9/7.8	166/161
96.30	n	0.66	7.5/11.5	6.3/3.3	43/40	56.5/52.5	1.5/1.5	9.2/9.5	135/140

14/27/0.85/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.00	n	0.83	5/7	15.3/4.5	37/39	-	-	11.4/9.6	140/147

15/27/1.18/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
2.15	n	0.74	5.5/5.5	8.1/16.4	35/31	39.6/35.9	5.0/6.3	16.7/17.0	139/149
2.15	n	1.67	5.5/8.5	16.4/5.0	31/35	35.9/39.3	6.3/5.8	- / -	149/138

16/27/1.03/F/S/fl/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.40	n	1.44	2.5/4	10.6/6.2	33/36	40.2/45.9	2.7/1.8	8.6/7.1	145/132
25.20	n	0.63	3.5/7.5	7.6/4.7	33/36	40.1/45.1	2.6/2.5	8.9/12.6	148/145
25.20	n	1.06	7.5/4.5	4.7/7.4	33/38	40.1/45.1	2.6/4.5	8.9/11.6	145/160
51.20	n	0.66	- / -	- / -	41/43	48.0/48.7	3.2/4.0	11.7/8.5	- / -
75.20	n	1.22	7/5.5	6.6/11.0	50/32	61.1/41.6	2.2/4.2	16.9/7.4	172/165
199.00	n	1.91	4/8	4.5/3.8	33/52	41.9/57.3	1.8/2.2	10.5/5.0	148/145

17/27/1.10/M/S/fl/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
4.00	n	1.83	2.5/2.5	17.7/16.6	23/21	-	-	8.5/11.1	129/130
22.00	n	1.80	4/4	14.2/17.6	30/34	-	-	5.0/6.9	164/162
52.00	y	1.70	3/5	3.3/4.4	38/40	-	-	8.8/8.4	148/156
69.30	y	1.43	4/6	5.7/1.6	35/49	-	-	10.0/13.1	130/139
93.30	y	1.64	3/5.5	3.4/3.6	34/45	-	-	11.4/9.9	146/145
124.00	n	1.03	3/7.5	5.3/11.2	35/35	41.7/40.7	5.5/3.8	9.2/10.5	143/130
144.00	n	0.80	8.5/10.5	5.7/5.8	34/42	39.9/49.1	4.1/2.5	13.5/12.1	148/145
165.00	n	1.81	7.5/8.5	4.5/7.3	40/36	53.0/49.9	4.8/3.2	7.2/7.9	129/130
189.00	n	1.08	5/5.5	6.3/5.7	34/43	42.0/51.8	3.3/5.0	8.5/7.8	134/158
261.00	n	0.81	5.5/6	2.8/3.5	48/56	57.7/72.8	2.0/3.8	5.3/12.1	120/135
340.00	n	1.25	3/4	4.7/8.4	42/50	49.5/66.8	4.8/6.4	6.3/15.6	153/171

18/27/0.92/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
12.30	n	1.00	3/4.5	3.5/10.9	24/27	30.1/34.3	2.3/6.0	8.5/8.5	131/139
28.30	n	1.13	5/6.5	5.3/5.6	34/37	41.8/48.1	3.3/5.9	7.1/4.8	134/139
28.30	n	0.64	6.5/9.5	5.6/1.9	37/39	48.1/49.7	5.9/3.0	4.8/6.9	139/142
52.30	n	1.16	4.5/4.5	6.1/4.1	32/34	38.1/40.7	2.5/4.3	11.2/12.0	159/148
52.30	y	0.68	4.5/7	4.1/8.3	34/40	40.7/48.4	4.3/1.9	12.0/13.7	148/156
79.30	n	1.06	4.5/9.5	8.6/8.0	32/38	39.2/49.6	5.4/3.8	11.2/10.6	166/157
124.30	n	1.88	8/12	5.1/5.8	30/30	38.7/39.2	4.9/4.4	13.1/13.1	129/145
156.30	n	1.51	5.5/11.5	5.2/6.0	30/35	41.4/44.8	4.3/3.8	10.8/7.7	136/142

19/27/1.06/M/S/fl/pvi/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
4.30	n	0.68	2/3	9.7/12.6	20/24	-	-	10.1/12.9	127/124
17.00	n	0.72	-	-	25/34	-	-	8.4/5.3	-/-
42.00	y	1.15	5/6.5	3.5/2.4	36/32	-	-	8.6/9.6	169/177
64.00	y	0.90	5.5/4.5	3.1/7.7	38/39	-	-	6.6/6.9	165/158
88.00	y	1.91	4.5/4	4.8/9.9	49/46	-	-	10.4/6.6	147/150
120.00	y	1.13	5.5/6	8.8/7.5	44/49	53.8/63.1	1.3/1.2	11.9/9.8	145/159
139.00	n	1.29	6/11.5	4.2/3.6	45/47	56.4/62.9	4.2/1.8	9.5/10.2	147/152
161.00	n	0.95	5.5/9.5	6.2/6.3	33/41	59.2/57.9	3.9/3.1	8.2/7.1	145/121
185.00	n	1.85	5/10	3.9/5.9	36/39	52.6/57.1	1.9/3.8	10.6/9.9	124/135
209.00	n	1.32	5.5/7	8.5/6.1	33/43	47.0/61.1	4.2/4.2	8.6/8.6	143/165
257.00	n	0.52	11.5/11	3.3/4.7	36/35	53.6/53.9	4.0/5.3	6.7/6.6	145/148
335.00	n	1.85	2/3.5	7.1/6.6	31/30	45.2/45.2	3.0/3.9	9.8/13.0	150/146

20/27/1.01/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.00	n	1.24	3/4	5.4/4.0	32/40	39.9/45.2	1.6/3.6	8.1/17.2	114/116
23.00	n	1.02	3.5/5.5	9.0/8.1	36/42	41.7/49.9	4.4/2.4	4.8/3.7	131/133
55.00	y	1.40	5.5/8	2.3/4.1	41/45	46.9/53.2	1.6/1.4	7.6/7.3	136/140
68.00	y	1.23	6.5/7	3.1/3.6	45/42	52.2/49.0	1.8/2.4	6.7/7.1	141/139
93.30	y	1.82	4.5/8	2.9/3.8	43/44	46.9/57.0	1.9/2.4	7.8/9.5	139/143
117.00	y	0.95	6/9	7.0/3.2	32/36	38.1/42.2	2.7/2.1	9.7/8.9	139/144
165.00	n	1.36	8.5/9.5	4.3/4.6	27/33	31.4/38.2	5.6/5.4	11.2/12.2	145/154
309.00	y	0.91	7/8	2.9/2.4	57/58	72.1/72.5	2.6/3.1	6.3/6.6	134/135

21/27/1.14/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
11.00	n	1.09	4/3.5	4.4/7.5	44/46	47.3/51.8	1.3/3.1	9.2/8.0	145/152

22/27/1.14/F/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.00	n	1.29	2.5/4	4.6/17.3	43/41	48.0/44.3	2.7/6.7	5.5/21.9	138/135
39.30	y	1.61	5.5/9.5	2.9/3.1	32/38	43.0/53.4	1.8/1.4	6.9/5.2	139/146
86.30	y	1.22	4/6.5	4.3/3.4	33/34	40.5/55.8	2.9/3.1	16.5/12.7	146/146

23/27/1.10/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
17.00	n	0.91	7/10	5.6/6.7	35/36	38.1/42.8	5.2/8.5	9.1/12.0	137/151
30.00	n	0.98	7/11.5	3.9/3.9	31/30	38.8/38.4	1.8/6.8	8.8/12.9	133/127
53.00	n	1.55	8/10.5	3.6/4.2	32/39	39.9/49.4	3.5/3.0	9.0/8.1	143/144
77.00	n	1.04	8/10	4.3/4.7	39/41	44.3/51.5	5.0/6.1	9.2/7.8	132/135

24/27/0.97/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
22.00	n	1.93	3.5/5.5	3.3/6.2	43/48	52.6/59.3	7.2/6.0	10.2/10.1	141/148
66.15	y	0.89	6.5/14	5.0/2.4	42/48	53.6/63.0	2.0/1.5	11.7/11.0	158/159
137.20	y	1.23	4.5/7	8.3/7.6	45/47	54.5/54.9	3.8/1.9	6.6/6.2	155/155
159.00	y	0.80	4/6	9.4/2.7	50/52	60.9/63.4	2.7/4.5	6.6/6.8	157/151
183.00	y	0.67	5/7.5	6.3/7.1	40/48	48.8/60.4	3.2/3.2	7.1/5.1	168/167
207.00	y	0.10	4/3.5	9.7/8.3	43/51	52.5/62.5	2.0/1.9	13.4/10.2	146/145

25/28/1.11/F/S/II

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
9.15	n	0.91	7/8	2.3/7.0	44/45	53.4/56.9	2.5/4.3	9.2/10.1	129/134
30.00	n	1.41	7.5/13	8.9/8.8	40/46	47.7/60.1	6.1/6.4	6.3/7.5	136/144
55.00	n	0.61	12.5/17	3.8/5.5	60/51	71.0/56.5	7.0/7.5	14.3/12.5	157/168
110.00	n	1.09	10.5/11.5	5.2/4.5	50/38	54.5/44.1	5.4/5.2	8.8/7.6	162/167

26/28/0.92/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.15	n	0.96	9.5/10.5	3.8/3.4	49/44	59.7/52.9	1.6/5.2	10.4/12.1	158/144
35.45	n	1.08	7/13	3.1/7.9	36/31	42.8/39.6	6.5/6.0	6.1/4.7	147/153
53.35	n	1.88	10.5/14	3.0/4.8	46/45	48.5/56.3	3.0/6.8	10.7/10.9	161/161

27/28/0.97/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
3.45	n	0.30	3.5/4.5	7.5/6.7	35/38	44.8/49.1	2.3/3.5	7.1/5.9	135/134
20.00	n	0.91	5.5/8	5.6/2.0	40/41	48.0/49.3	3.3/3.0	8.3/9.0	152/153

28/28/1.21/M/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.00	n	1.74	4.5/5.5	4.4/7.2	35/35	39.1/41.4	3.0/3.8	9.3/9.2	127/120
28.00	n	1.14	5.5/7	6.2/8.6	45/46	49.8/50.8	3.2/4.9	11.6/8.9	137/145
76.00	n	1.79	4.5/8	4.6/6.5	47/52	50.4/57.7	6.0/4.8	14.8/13.3	105/108
117.30	n	0.89	5/4.5	3.4/11.6	47/48	51.9/52.1	2.7/3.2	8.0/7.4	120/138
144.00	n	1.25	5.5/7.5	3.9/7.2	47/48	54.6/53.9	3.2/6.3	13.7/11.2	153/151
170.00	n	0.99	4/6	6.6/4.4	50/54	57.4/61.0	3.1/3.1	10.8/9.5	139/150
192.00	n	1.28	5.5/11	6.9/7.1	52/58	59.1/62.4	1.8/1.5	9.2/7.1	132/141

29/28/1.26/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.28	n	1.32	5/7.5	4.6/3.5	45/41	52.2/53.3	2.3/2.2	6.1/11.8	118/117
28.30	n	1.75	8.5/10.5	10.8/3.4	48/46	58.1/41.8	6.6/4.8	16.3/13.4	152/147
76.30	n	1.02	5/7	2.3/2.9	43/52	57.7/66.0	2.4/2.9	12.3/18.9	128/130
94.30	n	1.92	7/15	5.3/2.5	49/50	63.3/66.5	4.2/2.5	10.5/7.3	115/122
118.00	n	0.39	9.5/9	4.8/3.4	46/43	59.7/56.3	2.9/2.3	10.6/6.9	131/138
144.30	n	0.76	5/8.5	4.0/5.4	38/44	48.8/57.4	2.3/2.2	14.1/17.4	129/123

30/28/0.99/M/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.30	n	0.95	2.5/3	5.4/11.1	37/41	45.6/49.7	2.7/6.0	5.9/8.5	138/141
21.30	n	1.19	6/8.5	4.3/4.2	38/40	50.1/51.1	3.2/2.4	8.1/8.3	136/150
44.30	n	0.55	6.5/10.5	2.8/3.7	45/44	57.8/56.5	2.5/3.0	7.3/9.7	148/150
63.30	n	0.98	9/10.5	4.6/2.4	42/50	54.0/67.7	1.5/2.4	8.4/6.0	159/156
90.00	n	1.38	5.5/5	5.0/5.2	44/46	61.0/59.2	4.0/4.8	19.7/9.1	150/147
111.00	n	1.45	3.5/6	3.5/8.1	38/-	49.5/-	3.1/-	19.6/16.0	138/152

31/28/1.15/F/S/fl/pvl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
3.15	n	1.12	7.5/10.5	10.5/6.7	42/43	51.9/51.1	4.3/7.0	5.8/7.6	144/139
19.30	n	0.91	8.5/10.5	3.5/9.3	37/40	44.3/50.1	2.5/4.5	12.5/8.8	140/150
98.30	n	0.67	8.5/9	2.5/2.9	46/46	52.8/55.6	2.5/2.8	12.9/10.4	148/150

32/28/1.18/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
8.30	n	1.14	3.5/9	3.6/3.2	37/47	48.9/59.0	3.1/5.2	15.0/9.7	136/150

33/29/1.11/F/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
13.00	n	1.30	2.5/3.5	7.0/12.4	32/32	-/-	-/-	8.1/8.5	133/125
133.00	n	1.70	5/8.5	4.7/9.5	35/48	-/-	-/-	10.1/6.8	160/168

34/29/0.64/F/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.20	n	0.44	1.5/5.5	6.8/3.3	34/35	44.8/46.8	1.6/4.0	9.2/12.6	164/171
25.00	n	0.90	5.5/4.5	8.8/10.8	32/38	41.2/47.9	3.7/4.3	11.4/10.2	138/146
+++	n	1.49	10/14	3.3/8.2	52/62	71.6/86.6	3.9/5.7	-/-	-/-

35/29/1.42/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.35	n	1.64	6/5	3.9/6.7	32/30	36.5/-	6.3/-	22.3/26.0	150/155
6.35	n	1.14	5/3	6.7/7.3	30/32	-/38.2	-/4.6	26.0/24.7	155/158
36.00	n	2.00	8.5/8	4.8/13.4	-	-	-	-/-	136/168
84.00	n	0.92	5/11	4.9/4.9	45/50	51.0/57.2	2.3/2.9	15.5/11.1	126/126
109.00	n	0.66	8/5	4.2/16.2	50/67	59.8/74.6	2.1/7.5	7.2/9.5	130/151

36/29/1.90/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.30	n	1.58	3.5/4.5	3.8/7.8	42/43	53.2/50.4	2.2/3.2	9.0/9.0	130/136

37/29/0.89/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
9.00	n	0.98	5.5/7	3.7/3.9	34/34	40.2/39.1	2.7/2.7	10.3/6.8	109/114
21.00	n	0.82	5/6	7.5/4.7	36/34	40.5/38.8	2.8/2.3	6.9/7.1	114/114
51.00	n	0.71	3.5/9	10.1/10.3	40/36	43.1/39.1	2.2/4.9	9.1/5.6	154/154
93.00	n	1.37	7.5/15.5	5.9/2.5	34/35	36.2/38.9	3.3/4.3	11.2/7.0	158/158
189.00	n	1.56	6.5/11.5	10.9/3.5	35/35	55.2/48.5	2.6/6.0	9.3/5.4	176/156
261.00	n	1.45	13.5/15.5	3.2/4.7	41/48	57.8/69.5	3.1/4.0	11.3/8.4	126/156

38/29/1.61/M/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
14.00	n	0.79	4.5/2	12.2/12.5	38/38	43.6/46.5	2.1/4.1	7.7/6.6	164/154
36.00	y	1.14	4/9	5.2/4.2	40/47	49.7/53.7	2.3/1.8	8.0/7.8	116/138
60.00	y	1.99	6.5/9	2.8/9.1	46/46	58.2/59.6	3.3/2.0	8.9/9.3	131/133
202.00	n	1.36	6.5/9.5	6.6/10.8	55/64	70.2/84.7	4.9/3.1	10.7/10.9	161/177
229.00	n	0.56	4.5/11	6.3/9.9	40/49	55.4/65.4	3.2/4.0	6.6/7.1	131/130
345.00	n	2.42	8/17	6.1/1.6	38/52	57.6/68.0	3.9/4.8	10.6/8.5	167/158
369.00	n	0.88	6.5/8.5	9.2/4.0	35/52	47.5/66.9	2.3/5.9	6.3/7.8	

39/29/1.29/M/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
20.00	n	1.49	4.5/-	19.1/-	42/42	-	-	7.6/10.2	147/-
46.00	n	1.98	7.5/12.5	13.8/7.2	54/51	-	-	5.4/11.9	127/145

40/29/1.40/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
3.30	n	2.06	3.5/4	15.9/14.0	38/41	57.1/45.7	4/6.7	8.1/8.0	139/144
26.45	n	1.08	6/11	2.5/1.7	48/50	55.4/60.3	1.2/1.4	9.9/10.9	139/141
43.30	n	1.71	5.5/13	1.4/3.8	40/47	48.9/58.5	2.1/2.7	10.5/6.7	143/150

41/29/1.17/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
2.35	n	1.32	3/2.5	12.3/11.1	32/31	38.5/36.8	3.8/4.6	13.8/11.1	144/132
2.35	n	0.71	2.5/1.5	11.1/27.3	31/30	36.8/36.3	4.6/5.1	11.1/9.3	132/135

42/29/1.40/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
1.45	n	1.22	5.5/4	8.4/7.7	42/39	-	-	6.7/9.4	163/173
1.45	n	0.89	4/7.5	7.7/5.1	39/56	-	-	9.4/6.7	173/166
43.30	y	1.26	5.5/10.5	3.8/4.6	39/42	47.1/52.1	4.6/4.0	9.2/9.8	145/149
57.45	n	1.09	5/9.5	6.2/5.9	46/47	56.6/58.3	3.7/3.0	10.9/9.7	166/152
57.45	n	1.44	9.5/15.5	5.9/2.7	47/55	58.3/69.1	3.0/2.0	9.7/8.9	152/160
81.00	n	0.86	6/8	5.0/3.3	41/43	52.2/54.8	4.1/3.9	10.8/12.8	135/138
107.00	n	1.21	4/7	11.6/4.0	38/46	49.1/61.4	4.3/3.9	11.8/11.3	118/126
107.00	n	0.56	7/17	4.0/5.6	46/49	61.4/62.7	3.9/8.5	11.3/11.1	126/127

43/29/0.90/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.20	n	0.69	1.5/2	9.3/15.4	29/26	39.1/35.9	4.1/8.1	7.1/27.7	122/123
77.50	y	0.91	3/12	11.4/3.2	44/47	60.7/61.3	3.5/4.6	9.5/10.4	139/135
101.00	y	0.77	4/13	3.2/2.5	43/52	59.8/67.1	3.8/2.6	7.4/8.1	151/147
117.00	y	0.58	4/6.5	4.0/3.1	40/41	56.2/55.2	1.9/1.9	14.5/18.5	156/162
171.00	n	0.81	6/10.5	3.4/1.9	48/58	67.6/63.3	2.5/1.9	9.9/14.2	140/137

44/29/1.27/M/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
72.30	y	1.09	5.5/8	2.9/4.5	42/45	45.5/46.3	2.6/5.7	8.4/4.7	145/137
100.00	n	1.27	2.5/7.5	12.4/4.4	42/39	45.3/41.9	2.9/3.7	9.1/8.4	150/145
118.30	n	1.26	3/6.5	2.3/2.9	42/44	44.7/48.2	3.4/3.7	14.5/11.4	120/120
142.00	n	1.09	5/9	5.0/6.3	35/37	43.7/46.6	2.3/3.5	10.9/13.2	151/164
142.00	n	1.08	9/9	6.3/6.5	37/38	46.6/48.4	3.5/2.5	13.2/10.5	164/152
166.00	n	1.35	4.5/7.5	6.2/4.2	27/45	36.8/51.4	3.2/6.4	14.3/9.7	149/139
238.00	n	0.84	10/10	3.3/11.2	30/35	52.1/68.3	2.9/2.7	12.7/13.6	158/171

45/29/1.36/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
4.30	n	1.54	4/6	8.9/14.6	26/29	29.9/32.7	7.9/7.9	7.0/7.7	126/133
17.30	y	1.59	9.5/12	2.9/2.2	36/40	38.8/43.3	1.6/2.2	6.2/6.1	149/156
38.30	y	2.58	7/14.5	1.9/1.6	35/45	39.3/47.3	2.5/0.9	12.4/10.5	126/145
59.30	y	0.89	5.5/11	4.0/0.9	36/38	39.2/43.0	3.7/2.3	13.8/20.7	133/147
83.30	n	1.11	9.5/16.5	1.9/1.8	48/50	52.2/53.8	1.7/2.6	11.8/11.0	138/141

46/29/1.34/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
64.30	n	1.66	6/9.5	4.5/3.3	45/47	54.6/60.8	1.2/4.3	8.8/10.9	143/138
81.30	n	0.84	8/11.5	7.3/3.7	44/54	57.2/69.4	3.2/3.3	12.5/13.1	166/158

47/29/1.39/F/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
36.30	y	0.70	5.5/7	2.9/1.8	30/31	39.4/40.2	2.4/1.8	6.4/6.4	154/152
61.30	y	0.50	6/10	2.2/2.4	42/45	45.7/58.5	4.2/3.1	12.6/12.3	159/154
79.30	y	0.40	8/14	3.7/3.7	38/41	49.8/53.3	3.5/2.1	8.5/8.6	136/139
150.00	n	0.60	4.5/5.5	6.5/3.9	27/34	38.3/52.1	4.6/3.5	11.3/13.3	143/142
225.00	n	0.80	4/4.5	13.1/8.6	33/36	44.6/51.8	4.0/1.8	6.1/11.8	131/125

48/30/1.18/F/S/fl/pvl/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.20	n	1.20	4.5/3.5	4.4/7.2	35/35	52.3/54.8	1.5/1.2	9.6/12.0	136/124
5.20	n	1.52	4.5/4.5	6.2/8.6	45/46	52.3/52.4	1.5/1.8	9.6/12.5	136/124
20.00	n	0.14	4/4	4.6/6.5	47/52	42.6/40.2	5.1/4.4	7.4/10.6	137/131
280.00	n	0.65	9/-	4.4/-	32/36	41.7/44.3	3.5/5.4	10.9/7.4	152/-

49/30/1.95/F/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
4.30	n	0.61	5.5/4.5	5.1/6.4	42/47	45.1/51.6	4.1/1.9	6.3/8.7	124/123

50/30/0.72/M/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.15	n	0.61	5/9	12.0/8.2	42/38	44.1/43.1	2.6/5.8	- / -	158/171
16.45	n	1.20	8/8	6.4/17.6	38/46	46.8/54.6	3.8/5.7	5.4/9.7	144/164
35.15	n	0.91	11/19.5	11.0/9.5	39/40	46.8/49.2	8.1/8.6	14.1/5.3	162/162
59.15	y	1.00	10/9	3.3/6.1	42/42	47.6/50.8	3.4/1.3	10.7/8.7	159/155
83.15	y	1.16	6.5/10	3.3/5.9	45/46	59.6/63.1	3.1/1.2	12.5/16.5	154/149

51/30/1.28/M/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
61.30	y	0.98	5/5.5	4.3/4.1	42/52	48.2/59.1	3.0/3.3	8.4/10.4	140/135
83.30	y	0.64	4.5/6	5.8/4.5	46/48	48.9/54.4	2.6/3.7	- / -	- / -
107.30	n	1.69	20.5/19	4.9/2.0	45/62	54.3/74.4	3.7/1.1	9.0/7.5	143/146
136.30	n	1.55	6/15	7.3/4.4	46/55	54.8/65.3	5.3/2.3	9.6/10.7	149/165
149.00	n	0.71	6/9	8.3/6.3	38/43	-/60.5	-/3.7	12.1/12.2	131/136
202.00	n	0.72	12.5/12	9.7/4.5	63/60	86.5/77.6	3.9/4.3	- / -	139/141

52/30/1.07/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.25	n	1.42	5/5	4.7/10.7	42/42	53.7/54.7	3.2/6.2	20.5/10.1	142/140
18.40	n	0.94	4/4	8.6/24.2	35/40	41.9/47.6	4.0/7.5	8.3/6.1	159/167
48.40	n	1.63	10/14	4.0/4.1	38/44	53.8/59.3	6.3/2.8	6.1/6.4	146/147
72.00	n	1.15	2.5/4	7.6/5.4	43/40	58.2/52.9	6.5/2.5	12.8/14.2	149/143

53/30/1.67/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.00	n	1.66	-	-	34/34	-	-	4.2/6.0	- / -
21.00	y	0.89	-	-	43/43	-	-	8.8/8.3	- / -
45.00	y	1.06	-	-	52/53	-	-	7.1/6.9	- / -
118.30	n	1.03	6/9.5	3.3/11.3	50/60	-	-	7.8/8.3	136/147
142.00	n	1.32	8/16.5	4.7/6.5	50/64	-	-	8.4/10.5	147/142
167.00	n	1.97	6/12	4.6/4.2	59/62	-	-	14.0/16.0	137/127

54/30/1.15/M/S/fl/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
50.45	n	1.05	5.5/6.5	4.2/7.6	44/49	51.4/57.3	3.5/5.1	8.4/8.9	137/145
75.45	n	1.35	4/8	2.5/2.8	38/40	47.8/48.2	6.4/5.2	12.0/12.3	156/146
89.00	n	0.83	5.5/10	4.4/2.4	34/43	44.1/50.8	3.4/19.3	12.0/8.6	164/161
185.00	n	1.27	5/9.5	7.1/5.8	42/45	55.1/54.3	4.3/7.7	12.1/22.1	160/154

55/30/1.45/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
34.00	y	1.37	4.5/8.5	4.7/2.4	50/48	60.2/60.4	2.1/1.7	10.8/14.5	153/137
52.30	n	0.87	6.5/13.5	2.0/3.4	40/38	52.5/47.2	4.4/3.0	8.3/8.9	123/129

56/30/1.50/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
71.00	y	1.14	4.5/5	10.4/5.0	44/47	50.0/55.8	2.2/1.6	12.0/7.9	153/147
96.00	y	1.67	-	-	41/45	51.4/55.5	1.9/1.7	10.3/9.3	- / -
124.00	n	1.09	6/8.5	6.3/4.6	44/46	53.1/57.2	4.5/1.5	8.9/8.1	136/144
143.00	n	0.93	7.5/8	5.1/6.3	42/49	50.5/61.8	2.4/3.7	8.9/8.5	126/135
167.00	n	0.70	5/7.5	6.9/9.2	47/50	61.9/64.1	3.3/2.9	10.4/10.8	138/138
235.00	n	0.36	9.5/15.5	7.9/2.4	51/66	59.1/72.0	2.5/3.2	9.6/8.7	150/152

57/30/1.55/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MAP pre/post	MSP pre/post	MSP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
7.00	n	1.18	5.5/6	10.7/17.2	37/36	41.3/43.7	4.1/6.0	6.8/6.2	159/157
22.40	n	1.24	6.5/7	3.7/32.1	44/42	49.5/52.8	5.0/2.8	10.0/6.2	135/153
32.40	y	1.20	7/11.5	6.2/2.5	39/45	48.0/57.0	4.6/1.8	7.2/5.0	146/156
51.40	y	1.10	4.5/8.5	4.7/2.0	44/44	56.2/57.6	3.0/1.0	- / -	- / -
74.50	y	1.60	6/12	2.8/2.7	32/38	45.8/53.7	1.5/1.1	10.6/8.7	135/135
92.50	n	1.03	8/9.5	5.3/2.7	34/42	48.1/58.7	4.0/1.3	8.8/6.8	142/144

58/30/0.93/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
9.00	n	1.78	4/3	13.6/9.5	33/30	37.4/36.8	12.4/5.7	12.7/11.1	171/142

59/30/1.00/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
4.47	n	0.76	1.5/2.5	8.6/5.6	42/43	44.0/54.5	3.0/3.6	6.3/10.9	122/123
17.25	n	1.10	2.5/3.5	5.5/11.0	36/37	45.9/47.0	1.9/5.2	13.7/8.4	123/121
41.25	n	1.11	3.5/7.5	15.0/5.9	36/37	43.6/45.6	3.3/4.8	7.9/9.7	132/130

60/30/1.58/M/D/fi/pvi

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
19.00	y	0.95	2.5/4	6.7/4.1	39/41	50.8/51.8	1.5/1.3	10.3/9.2	125/133
115.00	y	0.95	3.5/4.5	4.2/3.0	57/57	78.0/79.3	2.3/1.6	13.7/11.5	162/158
186.00	y	1.25	6/6.5	4.9/3.9	46/50	70.5/78.0	4.1/2.2	8.6/8.0	149/149

61/30/1.43/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
28.00	n	2.45	4/16	15.1/4.1	36/40	-	-	7.0/3.6	155/165
145.00	n	0.50	6/7	6.0/6.4	28/32	-	-	9.5/9.9	152/144

62/30/1.42/M/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
34.40	y	1.06	4.5/5.5	4.3/2.6	33/38	39.6/46.4	2.2/1.1	10.5/10.2	158/145
58.40	n	0.88	4.5/10	13.7/11.5	48/58	49.5/57.6	4.4/6.0	9.4/10.1	180/175

63/30/1.07/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
12.00	y	0.84	4.5/10.5	6.2/2.7	46/51	51.7/57.7	3.7/2.0	8.8/9.4	154/156

64/31/1.20/F/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
55.00	n	0.45	6/12	11.8/4.7	48/47	53.3/51.9	2.3/3.0	12.0/14.8	153/142
66.00	n	1.56	10.5/21.5	1.4/5.5	55/60	62.3/68.0	1.8/6.0	12.2/8.2	151/149
96.00	n	0.64	7/7	5.7/7.2	59/64	66.6/72.5	2.4/3.4	8.0/16.5	174/161

65/31/1.64/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
12.30	n	1.44	5/5.5	4.7/12.0	33/33	42.9/43.2	2.5/5.0	7.9/9.2	141/130
29.30	y	0.95	7/9.5	3.7/1.6	40/46	50.6/60.3	4.2/2.4	8.5/9.8	148/148
48.00	y	1.76	7/7	1.6/4.0	43/49	56.7/64.7	2.3/1.4	8.5/9.3	156/165
72.00	n	0.92	4.5/7	3.5/1.7	43/55	56.2/72.7	2.3/2.3	8.1/9.5	149/142

66/31/1.88/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
13.30	n	0.97	3.5/6	8.6/14.1	37/37	42.9/42.2	3.9/11.4	8.6/11.5	156/154
30.00	y	1.16	6/9	1.7/2.6	55/50	60.9/55.0	1.8/1.8	8.4/8.6	175/172
49.00	y	0.72	5/6.5	5.1/8.9	52/56	57.5/63.2	4.0/1.8	10.7/9.8	169/171
75.00	n	0.96	12/16.5	2.3/1.6	50/54	60.1/64.4	2.9/2.4	9.0/9.0	146/155
98.00	n	1.51	5/12.5	8.1/4.1	46/44	-	-	9.7/9.5	156/156

67/31/1.56/F/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
8.00	n	0.99	3/4	9.1/14.4	42/40	49.9/51.4	3.7/13.5	9.3/9.7	147/143
13.00	n	1.57	4.5/6	7.7/17.2	41/38	52.4/47.9	3.1/9.5	8.8/7.2	143/149
32.00	n	0.60	4/9.5	3.8/7.9	45/42	57.2/53.1	2.8/8.8	9.7/4.2	140/154
56.00	y	1.00	9/12	5.7/2.4	52/57	67.0/72.9	2.1/1.6	- / -	161/163

68/31/1.47/M/D

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MAP pre/post	MSP pre/post	MSP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
4.05	n	1.71	4.5/4.5	11.8/6.4	34/34	41.2/41.6	3.6/2.9	7.4/10.3	126/127
4.05	n	0.73	4.5/6.5	11.8/9.4	34/35	41.2/45.1	3.6/4.9	10.3/7.9	126/121
15.00	n	1.56	7.5/7.5	2.8/12.2	40/43	50.2/54.9	1.3/4.8	10.4/10.1	132/137
39.00	y	0.92	13/12.5	3.6/5.6	45/46	49.3/53.7	2.6/2.6	10.2/8.3	159/159

69/31/1.61/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
2.35	n	1.73	5.5/9	9.1/5.7	38/40	-	-	11.5/13.3	153/141

70/31/1.60/M/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.45	n	0.68	4/6.5	6.4/8.4	35/38	43.9/47.9	1.9/6.0	7.0/13.9	121/128
19.00	y	1.20	5/5.5	3.2/2.3	38/36	46.5/44.2	1.4/1.7	16.8/13.9	140/141
41.40	y	1.64	4/12	7.6/3.2	37/39	45.5/46.2	1.6/1.6	7.5/9.6	150/149
74.20	y	1.60	6/9.5	3.3/2.6	38/44	43.1/51.2	2.1/3.1	9.9/10.2	149/144

71/31/1.45/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
9.00	n	1.40	4/5.5	4.8/13.1	26/27	27.2/28.8	1.7/3.4	5.6/5.5	121/114
33.20	y	0.75	4.5/9	4.2/5.2	50/54	51.3/53.9	2.0/1.5	8.2/7.7	170/173
64.20	n	1.27	10.5/11.5	4.0/5.5	53/52	61.4/60.0	3.0/2.4	8.7/8.3	128/131
64.20	n	0.75	11.5/12.5	5.5/3.5	52/47	60.0/53.4	2.4/4.6	21.4/16.1	131/154

72/31/1.99/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
30.30	y	0.31	4.5/5.5	4.7/2.0	45/47	56.1/58.3	1.3/1.0	8.6/8.8	150/150
58.00	y	0.68	5.5/15	2.8/3.7	56/61	58.5/73.1	1.2/1.1	7.9/7.8	143/153
70.00	y	0.98	7/12.5	2.9/8.1	50/50	60.3/59.1	1.9/1.0	7.4/6.8	146/142
94.00	n	1.40	5/11.5	8.4/2.7	52/55	59.5/63.4	4.7/4.0	13.9/13.5	148/152
118.00	n	0.68	-	-	55/54	60.2/57.6	4.5/6.0	10.6/9.7	-/-

73/32/1.14/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
2.45	n	0.86	6.5/6.5	3.0/2.8	40/39	48.5/45.2	1.4/2.1	26.9/23.0	115/115

74/32/2.07/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
27.10	n	1.40	7/10	8.8/12.5	36/37	40.5/45.8	4.3/7.6	8.1/6.5	149/157
51.10	y	1.65	6/14	2.4/2.6	37/47	46.8/57.8	1.1/1.9	9.3/9.8	153/159
87.00	n	1.19	6/12	4.1/1.5	34/43	45.9/58.8	2.2/1.5	10.6/10.2	151/148
117.00	n	1.93	6/11	7.2/10.1	54/68	64.6/80.3	1.8/5.6	8.7/12.4	143/176

75/32/2.00/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
27.10	n	0.79	7.5/9.5	9.4/14.6	36/47	41.0/61.4	4.2/7.6	7.6/6.6	163/154
50.30	y	1.57	5.5/12.5	3.9/1.7	41/53	50.7/61.0	4.4/1.3	8.1/9.8	162/158
78.00	n	0.90	8.5/12.5	4.8/6.3	46/50	56.7/57.2	5.2/5.2	16.3/13.6	132/147

76/32/2.07/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.30	n	0.69	3/5	13.6/6.8	34/43	37.1/49.3	2.4/3.8	7.9/7.3	130/128
14.00	y	0.93	5.5/8	5.2/5.9	50/53	60.4/69.5	1.4/1.8	7.5/8.0	148/159
39.00	y	0.84	4.5/6	4.8/5.7	53/55	60.9/63.1	2.2/2.1	8.8/8.3	159/152
63.00	n	1.96	4.5/9	8.6/4.7	52/51	59.7/66.2	4.1/4.6	12.3/18.1	150/145

77/32/1.79/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.00	y	1.19	1/5	11.7/10.2	40/50	44.0/56.2	1.9/4.1	11.8/12.2	162/167
15.00	y	1.45	6/6.5	7.3/2.1	45/50	51.2/59.5	3.1/1.1	9.4/9.1	168/171
44.00	y	1.77	6/8	5.7/3.3	45/50	58.3/63.8	3.8/1.0	10.1/10.6	169/165
64.00	n	1.80	4/10.5	5.3/2.5	43/46	49.9/57.8	2.7/3.6	9.7/12.3	160/161
92.00	n	2.02	8.5/9	14.1/8.1	45/45	57.0/56.6	4.2/6.4	9.0/6.7	158/158
134.00	n	0.72	8/15.5	5.1/6.9	41/48	53.4/64.9	4.2/2.9	6.6/8.3	155/133
230.00	n	0.72	13/14	4.9/3.4	45/48	53.3/56.7	3.2/4.3	9.2/8.6	156/174
302.00	n	0.97	11.5/17.5	3.9/4.3	62/66	73.8/78.7	2.8/1.7	10.4/9.7	142/147

78/32/1.72/F/S/fl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
3.45	n	1.81	3.5/6	8.7/13.7	37/40	40.1/53.4	1.9/6.0	17.0/12.6	142/144
27.00	n	2.01	9/8	4.7/8.0	53/45	66.2/53.5	2.0/6.8	6.5/16.7	131/144
37.00	n	1.62	7.5/7.5	3.1/4.8	55/48	68.3/59.6	4.3/3.6	9.1/11.3	140/150
61.00	n	1.28	8/12.5	2.1/5.3	59/49	67.4/55.4	2.5/4.5	11.8/14.9	144/151
93.00	n	1.79	6.5/10	6.1/4.0	38/34	45.8/45.3	2.7/4.3	13.5/16.1	128/132
115.00	n	0.81	6.5/10	2.9/2.6	33/36	44.4/47.7	3.0/2.8	18.4/16.5	119/121
133.00	n	0.65	11.5/11	2.7/3.2	38/39	49.0/50.4	3.5/5.5	8.9/16.2	135/146

79/32/2.07/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.50	n	2.64	3/8.5	9.0/9.5	43/48	52.2/59.5	4.1/6.0	13.3/15.1	127/141
25.20	n	1.89	5/8	13.7/24.5	46/50	55.5/64.3	7.2/10.5	7.4/4.4	145/154
69.20	n	1.11	5/5.5	3.7/18.4	43/50	50.0/58.9	3.0/4.3	7.4/8.0	122/143
88.30	y	0.33	4/9.5	8.7/5.1	50/64	61.6/73.1	4.5/13.1	10.0/9.5	144/132
111.30	n	0.43	5/8	13.3/3.3	49/54	59.7/70.8	2.6/3.6	12.4/11.5	122/123

80/32/0.60/M/S/fl/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
77.30	n	0.88	4/4.5	3.4/6.1	45/45	58.5/58.4	0.9/1.4	10.3/10.5	127/129
94.15	n	0.81	2.5/2	7.0/17.8	33/35	44.1/48.1	1.8/2.6	11.5/10.6	129/136
116.00	n	0.70	4/3	11.1/8.5	31/32	44.2/46.4	5.3/4.2	10.6/9.6	144/140
140.00	n	0.64	5/7	7.2/3.5	32/33	47.8/49.6	3.1/3.7	9.4/8.4	147/157
162.00	n	1.46	7/8	5.5/7.5	35/45	48.2/64.9	2.3/6.0	5.5/9.0	149/171

81/32/2.27/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
77.00	y	1.85	9/11	1.2/2.4	49/46	56.7/51.0	1.8/2.1	13.4/15.4	135/143

82/32/1.60/M/S/pda

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
7.20	n	0.84	1.5/3	12.8/9.9	34/36	-	-	7.9/8.2	131/133
20.00	n	0.78	2.5/-	10.4/-	42/40	-	-	7.3/3.3	133/-
53.00	y	0.35	6/7	9.1/7.3	43/42	-	-	4.4/5.4	156/154
68.00	y	1.30	5/6	7.6/4.6	47/54	-	-	5.2/5.9	151/145
112.00	y	1.72	7.5/9.5	5.7/5.2	47/50	-	-	8.6/8.9	153/160
136.00	y	1.29	9.5/12	2.7/2.1	47/55	-	-	7.4/8.9	126/127
162.00	n	1.64	10/12.5	5.4/3.6	45/49	-	-	7.4/9.8	136/138

83/32/1.78/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
93.00	y	0.68	7/12	5.4/2.8	49/43	59.5/64.1	2.5/3.1	7.9/6.9	133/131
113.00	n	0.73	5.5/7.5	8.1/7.8	44/49	57.1/63.9	4.5/4.1	8.1/9.2	145/131
137.00	y	1.15	9.5/18.5	5.3/2.7	48/58	61.5/75.9	2.0/1.0	7.2/6.3	159/137
161.00	n	1.43	6/11	4.6/6.0	58/61	70.8/79.7	9.9/3.1	9.3/11.5	133/130
185.00	n	1.73	7/15	3.4/3.1	52/54	67.6/72.9	3.3/3.4	10.9/11.4	136/130

84/32/2.14/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.00	n	0.14	6/-	9.5/-	42/-	42.9/-	2.2/-	13.1/15.5	118/-
168.00	n	1.02	5.5/5	6.2/14.7	42/48	50.7/58.5	1.5/8.5	12.5/11.7	126/137

85/32/1.63/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.16	n	1.10	4.5/3.5	7.7/14.2	44/46	48.1/48.1	8.6/6.4	7.9/7.6	130/143
20.16	y	0.41	12/13.5	2.5/2.1	42/44	68.6/72.5	1.5/1.5	7.7/7.7	161/156
80.16	y	1.31	7/8.5	3.7/2.9	65/68	94.8/99.4	0.9/0.7	13.0/11.4	151/145
100.00	y	0.62	6/8.5	2.3/1.6	63/57	82.1/85.9	1.3/1.1	9.0/7.9	120/114
162.00	n	0.78	11/11	6.7/11.0	50/53	74.4/76.4	5.5/4.7	9.9/18.1	121/136

86/33/1.99/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.00	n	1.09	1/2.5	11.7/6.8	30/34	32.2/44.7	6.1/3.7	10.2/8.8	127/119
19.00	n	0.86	3.5/4	11.4/17.5	30/39	36.2/46.2	6.6/10.6	11.3/8.5	128/149
69.00	n	1.70	6/9	3.4/6.4	33/26	46.1/46.2	5.7/4.4	7.8/9.2	134/136
87.00	n	1.93	5/6.5	12.2/13.0	32/32	43.7/43.6	2.4/3.9	8.0/15.3	142/140

87/33/1.80/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
8.20	n	0.32	2.5/7	5.2/4.0	42/44	-	-	6.9/7.5	119/116
12.00	n	0.97	-/-	-	41/40	-	-	7.0/8.7	-/-
29.00	n	0.43	6.5/6	6.5/8.0	32/34	-	-	8.6/7.8	130/135
51.30	n	1.43	7/10.5	2.2/4.5	33/40	-	-	7.5/7.5	149/143
84.00	n	0.59	6/-	6.1/-	47/43	-	-	11.0/11.2	123/-

88/33/1.83/F/S/fl/pvl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.30	y	1.43	4.5/10	3.2/2.0	42/44	-	-	7.7/7.9	165/156
24.40	y	1.10	-	-	48/55	-	-	9.5/8.6	-/-
49.30	y	2.33	8/10.5	4.8/1.3	58/62	-	-	9.6/8.0	156/146
73.15	y	2.13	7.5/16.5	2.1/1.4	60/67	-	-	7.5/8.2	136/136

89/33/1.70/F/S/fl/pvl

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
57.35	n	0.83	11/15	3.8/4.4	54/57	69.9/77.3	2.6/4.2	12.1/12.1	144/145
79.35	n	1.37	12/20	2.9/3.3	52/64	69.6/85.2	2.0/3.2	10.5/11.3	148/162
150.00	n	1.42	8/13.5	9.6/4.4	50/52	64.5/66.2	4.7/3.2	9.4/8.2	132/145

90/33/1.61/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
5.20	n	1.76	4/5.5	2.6/3.8	37/40	45.7/49.8	1.7/3.3	8.0/13.2	113/117
28.30	n	1.09	6.5/4.5	8.4/5.5	40/40	48.7/46.4	3.4/9.4	5.3/6.0	138/161
53.30	n	0.72	5.5/8.5	2.9/7.6	41/44	48.1/52.5	3.7/5.6	7.8/7.4	140/143

91/34/1.76/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
11.00	n	2.14	3.5/3	2.7/24.4	39/44	49.8/58.9	2.2/9.4	5.8/6.8	122/138
30.00	n	2.01	5/5	13.8/8.3	37/41	40.4/45.3	2.5/3.9	15.3/12.3	141/132
54.00	n	2.14	8/8	3.1/7.5	45/40	55.3/50.2	2.9/5.2	11.3/9.9	134/160

92/34/1.84/F/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
11.45	n	0.81	7/-	6.5/-	-	-	-	6.9/9.2	133/-
27.45	n	1.40	6/9.5	11.7/12.0	37/36	50.2/46.1	6.1/6.0	10.3/6.5	139/145
72.00	n	0.59	5/9.5	6.7/4.2	48/45	60.5/56.2	4.6/6.7	14.5/11.7	128/132

93/34/2.48/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
3.00	n	1.39	4.5/4.5	12.3/15.7	36/32	-	-	8.1/8.8	124/120
18.00	y	1.93	4/10.5	5.2/2.9	43/56	-	-	7.6/7.9	148/150
41.00	y	2.39	6/9	5.8/3.5	52/54	-	-	5.8/8.5	140/142
62.00	y	0.79	4.5/5	7.0/8.0	46/52	-	-	8.6/9.6	139/139
91.00	y	1.86	3.5/12.5	7.1/1.5	56/54	-	-	7.2/8.4	135/141
116.00	n	0.27	-	-	50/46	-	-	11.8/9.2	-/-

94/34/2.42/M/S

Age hrs.min	Par. y/n	$\Delta PaCO_2$ kPa	Mean Vel pre/post	Vel CoV pre/post	MABP pre/post	MSBP pre/post	MSBP CoV pre/post	PaO_2 (kPa) pre/post	Heart Rate pre/post
6.00	n	2.30	10.5/11.5	2.3/3.2	28/29	43.3/44.0	4.2/8.3	10.0/7.4	102/103
25.30	y	1.94	10/10.5	4.3/2.1	31/33	40.7/43.8	2.6/1.4	5.5/9.3	110/113
45.30	y	1.26	10/12	3.7/3.6	42/44	50.8/56.2	2.1/3.3	7.4/7.3	124/126
69.00	y	1.23	9/10.5	2.5/2.3	59/67	66.7/82.0	1.5/1.8	10.2/9.3	149/155
93.00	y	1.25	7/15.5	3.7/6.0	59/71	74.9/89.2	3.2/1.4	8.9/8.2	161/177

Appendix 4

Raw Data for Chapter 8

Clinical details and changes in stroke distance and heart rate in ventilated preterm infants following a 1 kPa rise in $PaCO_2$.

Infant	Sex	Gestation	Weight (kg)	Outcome
1	M	26	1.15	S
2	M	27	1.15	S
3	M	28	0.99	S
4	M	28	1.18	S
5	M	29	1.90	D
6	M	29	1.27	S
7	F	29	1.39	S
8	F	29	1.95	D
9	M	30	1.15	S
10	M	30	1.58	D
11	M	30	1.42	S
12	M	31	1.64	S
13	M	31	1.88	S
14	F	31	1.56	D
15	M	31	1.60	S
16	M	31	1.99	S
17	M	32	2.07	S
18	M	32	2.07	S
19	M	32	1.79	S
20	M	32	1.78	S
21	M	34	2.42	S

Details of infants in CO_2 /cardiac output studies (S=survived, D=died).

Study 1

Infant	Age hrs	$\Delta PaCO_2$ (kPa)	Par y/n	MABP (mm Hg) pre	MABP (mm Hg) (1)	MABP (mm Hg) pre (2)	MABP (mm Hg) post	Stroke distance (m) pre	Stroke distance (m) (1)	Stroke distance (m) pre (2)	Stroke distance (m) post	Heart Rate pre	Heart Rate (1)	Heart Rate pre (2)	Heart Rate post	PaO_2 (kPa) pre	PaO_2 (kPa) post
1	6	0.82	n	42	42	42	0.08	0.08	0.08	134	139	127	13.8	9.5
2	67	1.44	y	43	43	54	0.04	0.04	0.03	168	167	164	5.9	7.8
3	6	0.95	n	37	38	41	0.08	0.09	0.07	141	120	141	5.9	8.5
4	9	1.14	n	37	37	47	0.08	0.07	0.09	136	155	153	15.0	9.7
5	7	1.58	n	42	41	43	0.09	0.08	0.06	129	143	135	9.0	9.0
6	73	1.09	y	42	42	45	0.11	0.11	0.08	143	148	137	8.4	4.7
7	37	0.70	y	30	30	31	0.05	0.05	0.05	170	170	163	6.8	6.8
8	5	0.61	n	42	44	47	0.08	0.08	0.07	124	125	123	6.3	8.7
9	89	0.83	n	34	33	43	0.09	0.08	0.09	162	169	161	8.6	12.0
10	115	0.95	y	57	57	57	0.09	0.09	0.08	165	164	157	9.6	11.5
11	35	1.06	y	33	33	38	0.10	0.10	0.10	164	157	145	10.5	10.2
12	30	0.95	y	40	41	46	0.08	0.07	0.08	147	169	148	8.5	9.8
13	30	1.16	y	55	54	50	0.04	0.05	0.05	180	161	172	8.4	8.6
14	13	1.57	n	41	41	38	0.12	0.12	0.12	144	142	149	8.8	7.2
15	19	1.20	y	38	39	36	0.09	0.09	0.09	141	140	149	16.8	13.9
16	31	0.31	y	47	47	45	0.11	0.11	0.09	150	149	150	8.8	8.6
17	87	1.19	y	34	34	43	0.08	0.07	0.06	153	169	146	8.1	6.5
18	6	0.69	n	34	35	43	0.05	0.05	0.05	130	128	129	7.9	7.3
19	6	1.19	y	40	41	50	0.06	0.05	0.04	164	160	167	11.8	12.2
20	93	0.68	y	49	47	53	0.11	0.11	0.07	133	135	132	7.9	6.9
21	46	1.26	y	42	40	44	0.07	0.07	0.08	120	121	123	7.4	7.3

Study 2

Infant	Age hrs	$\Delta PaCO_2$ (kPa)	Par y/n	MABP (mm Hg) pre (1)	pre (2)	post	Stroke distance (m) pre (1)	pre (2)	post	Heart Rate pre	(1)	pre (2)	post	PaO_2 (kPa) pre	post
3	22	1.19	n	38	37	40	0.09	0.09	0.09	141	131	150		8.1	8.3
6	100	1.27	n	42	42	39	0.12	0.10	0.09	149	151	145		9.1	8.4
7	62	0.50	y	42	41	45	0.05	0.05	0.05	162	157	154		12.6	12.3
12	48	1.76	y	43	44	49	0.05	0.05	0.07	155	158	166		8.5	9.3
13	49	0.72	y	52	51	56	0.04	0.04	0.04	170	170	171		10.7	9.8
14	32	0.60	n	45	45	42	0.12	0.12	0.11	144	137	141		9.7	4.2
15	42	1.64	y	37	37	39	0.12	0.13	0.15	151	151	149		7.5	9.6
16	58	0.68	y	56	56	61	0.10	0.10	0.10	142	144	154		7.9	7.8
18	14	0.93	y	50	50	53	0.09	0.08	0.07	151	146	159		7.5	8.0
19	15	1.45	y	45	44	50	0.06	0.06	0.06	171	166	171		9.4	9.1
21	69	1.23	y	59	60	67	0.06	0.06	0.07	141	142	149		10.2	9.3

Study 3

Infant	Age hrs	$\Delta PaCO_2$ (kPa)	Par y/n	MABP (mm Hg) pre (1)	pre (2)	post	Stroke distance (m) pre (1)	pre (2)	post	Heart Rate pre	(1)	pre (2)	post	PaO_2 (kPa) pre	post
3	45	0.55	n	45	45	44	0.09	0.07	0.06	143	153	150		7.3	9.7
12	72	0.92	n	43	44	55	0.07	0.07	0.08	150	149	140		8.1	9.5
13	75	0.96	n	50	50	54	0.10	0.09	0.10	145	145	148		9.0	9.0
16	70	0.98	y	50	50	50	0.11	0.10	0.09	147	145	142		7.4	6.8
18	39	0.84	y	53	52	55	0.09	0.09	0.06	162	157	152		8.8	8.3
21	93	1.25	y	59	59	71	0.06	0.06	0.07	182	176	177		8.9	8.2