BLOOD FLOW AND BEHAVIOURAL STATES IN THE HUMAN FETUS

BLOEDDOORSTROMING EN GEDRAGSPATRONEN IN DE HUMANE FOETUS

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Chapter 1

INTRODUCTION

1.1 Historical background

Since Fitzgerald and Drumm (1977) first reported on the measurement of blood flow velocity in the umbilical cord by means of continuous wave Doppler ultrasound, our knowledge of the human fetal cardiovascular system has rapidly expanded. Measurements on volume blood flow in umbilical vein and fetal descending aorta using pulsed wave Doppler ultrasound were first described by Gill and Kossoff (1979) and Eik-Nes et al (1980). However, errors that arise from single measurement of vessel diameter and fetal weight estimations by ultrasound have resulted in attention turning to two alternative methods of assessing fetal blood flow. First, combined analysis of the blood flow velocity and pulsatile vessel diameter waveforms for more accurate calculation of volume flow in the lower part of the fetal descending aorta (Tonge et al, 1983). It was demonstrated that the marked rise in aortic stroke volume (= pulsatile flow integrated over one cardiac cycle) during normal late pregnancy is entirely correlated with the pronounced increase in aortic diameter. Moreover, it was calculated that the percentage of total cardiac stroke volume directed to the descending aorta varies between 65 and 80%. Second, calculation of angle-independent parameters such as the A /B ratio, Resistance Index and Pulsatility Index. A /B ratio (Stuart et al, 1980) is defined as peak systolic flow velocity (A) divided by end diastolic flow velocity (B). Resistance Index (Planiol and Pourcelot, 1975) is derived by dividing the result of the peak systolic flow velocity minus the end diastolic flow velocity by the peak systolic flow velocity. Pulsatility Index (Gosling and King, 1975) is derived by dividing the result of the peak systolic flow velocity minus the end diastolic flow velocity by the averaged flow velocity. Calculation of angle independent parameters was performed in the lower thoracic part of the fetal descending aorta (Griffin et al, 1984; Jouppila et al, 1984; Tonge et al, 1986b), umbilical artery (Stuart et al, 1980; Reuwer et al, 1984; Trudinger et al, 1985b) and fetal common carotid (Marsal et al, 1984a, Arabin et al, 1987) and internal carotid artery (Wladimiroff et al, 1986). For a correct interpretation of recorded data it is of importance to establish the effect of internal variables, e.g. fetal breathing movements, fetal heart rate and rhythm and fetal behavioural states. Blood flow velocity waveforms in the fetal descending aorta, umbilical artery (Marsal et al, 1984b) and internal carotid artery (Wladimiroff and Bel, 1987b) are clearly modulated by fetal breathing movements. In a study of fetal cardiac arrhythmias (atrioventricular blocks and supraventricular tachycardias) Tonge et al (1984a, 1986a) were able to confirm an earlier report by Marsal et al (1984b) that despite alterations in rhythm, blood flow in the fetal descending aorta is maintained within the normal range. Concerning the ontogeny of behavioural states in the human fetus, Nijhuis et al (1982) were able to demonstrate in multiparous women that fetuses of 37-

38 weeks of gestation had developed behavioural states which in their organization are comparable to the states in full-term neonates (Prechtl et al, 1964, 1985). They selected three independent "state" variables, i.e. fetal heart rate pattern (excluding accelerations during movements), eye movements present or absent, and gross body movements present or absent.
Fetal behavioural states have also been studied in growth-retarded fetuses. According to Van Vliet et al (1985b), development of behavioural states in these fetuses is retarded.

1.2 Objectives

The objective of the present study was five-fold:
The first objective was to establish in normal pregnancy a possible relationship between the flow velocity waveform in the fetal descending aorta and fetal behavioural state, in particular states 1F and 2F according to the classification of Nijhuis et al (1982). These two behavioural states were studied because of the high incidence of 1F (32%) and 2F (42%) at 38 weeks and the marked differences in fetal heart rate pattern, fetal eye movements and fetal body movements between these two behavioural states (Nijhuis et al, 1982). State 3F and 4F were excluded from the study because of the low incidence of these behavioural states, respectively 1% and 7% of the recording time (Nijhuis et al, 1982). Moreover during behavioural state 4F the fetus moves continuously too vigorous to obtain reliable blood flow velocity waveforms. Blood flow velocity waveforms were recorded at 37-38 weeks of gestation, since only then well-defined behavioural states could be expected (Chapter 3.1). The characteristic blood flow velocity changes in the fetal descending aorta observed during intrauterine growth retardation (IUGR) prompted a similar behavioural state related study in this high risk group and represented our second objective, the results of which can be found in Chapter 3.2.
Doppler flow measurements are increasingly performed during the early third trimester of pregnancy for the early detection and evaluation of intrauterine growth retardation.
The results obtained at 37-38 weeks justified a repeat of this study during the early third trimester of pregnancy. At 27-28 weeks of gestation there already is a clear periodicity of state variables, but there is no proper synchronization in their cyclic appearance, thus allowing elucidation of the role of separate variables on possible flow velocity waveform changes in the fetal descending aorta. This was the third objective of our study; the data are presented in Chapter 3.3.
Following the introduction of an ultrasound method for recording blood flow velocity waveforms in the fetal internal carotid artery (Wladimiroff et al, 1986), the fourth objective was to relate these waveforms to fetal behavioural states in normal pregnancy at 37-38 weeks of gestation. It was decided to also include the umbilical artery in the study, since flow velocity waveforms from this vessel are often documented with respect to the early detection of IUGR. From the results collected in this cross-sectional study on blood flow velocity waveforms in the internal carotid artery as well as the earlier observation that during the last four weeks of gestation the pulsatility index in this vessel displays a gradual

decline (Wladimiroff et al, 1987b), it was decided to also perform the behavioural state related study in the fetal internal carotid artery in a longitudinal design between 36 and 41 weeks of gestation. This would provide an answer to the question as to the role of fetal behavioural states in the fore-mentioned reduction in PI during late pregnancy. The results from the cross-sectional study are presented in Chapter 4.1, the results from the longitudinal study can be found in Chapter 4.2.

The fifth objective of our study was to elucidate the possible role of fetal behavioural states in fetal internal carotid artery and umbilical artery blood flow measurements during IUGR. We, therefore, first established the incidence and magnitude of flow velocity waveform changes in these two vessels in the presence of IUGR with particular emphasis on the PI umbilical artery /internal carotid artery ratio as a possible predictor of fetal growth retardation. Results are presented in Chapter 4.3. This was followed by a cross-sectional study at 37-38 weeks of gestation, during which blood flow velocity waveforms in both vessels in IUGR were documented during behavioural state 1F and 2F. The data from this part of the investigation can be found in Chapter 4.4.

Chapter 2

FETAL BEHAVIOUR, PARTICULARLY IN RELATION TO THE CARDIOVASCULAR SYSTEM: A LITERATURE SURVEY

Introductory remarks

In this chapter human and animal experimental data on the maturational aspects of fetal behaviour, particularly in relation to the fetal cardiovascular system will be reviewed.
Major progress has been made in the study of human fetal behaviour as a result of high quality real-time ultrasound equipment. A qualitative and quantitative description of fetal motor activity is now available from very early pregnancy onwards. Doppler ultrasound has allowed detailed studies on the development of fetal heart rate patterns as early as 10-12 weeks of gestation. Recurrent episodes of low and high heart rate variation are present as early as 27 weeks. At term so-called behavioural states closely resembling those observed in the newborn have been documented.
Intrauterine growth retardation (IUGR) is a sizable problem in obstetric care. Changes have been reported on both fetal blood flow and fetal behaviour during IUGR. Little information is available on possible changes in fetal blood flow relative to fetal behaviour.

2.1 Maturational aspects of fetal behavioural variables

Since the advent of ultrasound it became clear that the fetus of 8-10 weeks postmenstrual age moves spontaneously in utero. Reinold (1971, 1976) using a static compound B scanning system already recognized different kinds of movements in early pregnancy. A first comprehensive study of the quality of fetal movement patterns was presented by Ianniruberto and Tajani (1981). The description of the movement patterns was however not very specific. A first detailed account of the different movement patterns was provided by de Vries et al (1982); their classification was greatly influenced by previous research on preterm and fullterm infants (Prechtl et al, 1979). They describe the early emergence of different movement patterns resulting in 16 patterns at the age of 15 weeks. The periodicity of the various movements undergoes several changes. After 14 weeks bursts of movements are replaced by much larger epochs of fluctuating activities (De Vries et al, 1985, 1987). Quantification of fetal quiescence demonstrated that in between 8 and 19 weeks total absence of movements never lasts longer than 13 minutes.
During the second half of gestation increasingly rest/activity cycles can be observed (Dawes et al, 1982b). So far, quantitative assessment of fetal motility

has only been carried-out for general movements, breathing and hiccups. The median incidence of general movements varies between 10 and 16% (Manning et al, 1979; Roberts et al, 1980; Patrick et al, 1980; Visser et al, 1982) and for breathing movements between 6% at 20 weeks and 30% at 30 weeks, with a decline thereafter (Patrick et al, 1980; De Vries et al, 1984). New information is underway on the incidence of more isolated movements such as retroflexion / rotation and anteflexion of the head during the second half of pregnancy using two linear array real-time transducers (Roodenburg, personal communication).
Fetal movement counting has been suggested as a test of fetal well-being. Valentin (1986) included nearly 2000 women in a screening programme using maternal fetal movement counts for detection of fetal jeopardy. Daily 15-minute counting sessions and fetal movements charts with individual lowest normal limits of these movement counts were used. A decrease in fetal movements was defined as two consecutive movement counts below the lowest limit, i.e. the alarm signal. This signal was associated with an increased risk of the delivery of a small-for-date infant, congenital malformation, respiratory disturbance or hypoglycaemia.
Early maturation of fetal cardiac activity is characterized by an initial rise in fetal heart rate (FHR) from 120-180 bpm (Robinson and Shaw-Dunn, 1973) between 6 and 10 weeks, followed by a gradual decrease to about 140 bpm at 19 weeks. Beat to beat variation is minimal in the pregnancy period from 9½-15 weeks. In the period from 16-18 weeks, sometimes beat to beat variation is visible; from a duration of 19 weeks on, there is a continual distinct beat to beat variation (Wladimiroff and Seelen, 1973). Later both FHR accelerations and decelerations occur, the latter being more numerous until about 30 weeks; thereafter this relation is reversed (Visser, 1984). Related to the rest-activity cycles in fetal motility, recurrent episodes of low and high heart variation can be observed as from the late second trimester onwards (Martin and Schifrin, 1977; Wheeler and Murills, 1978; Timor-Tritsch et al, 1978; Junge, 1979; Visser et al, 1981; Dawes et al, 1982b). From this gestational age onwards FHR accelerations are clustered within episodes of high heart rate variation. Mean FHR is not significantly different in periods of low and high variation until 34 weeks (Dawes et al, 1982b). Thereafter mean FHR is higher during periods of general body movements as compared with periods without these movements. With increasing gestational age there is a rise in proportion of time spent in high FHR variation, to a plateau of 55% at 34 weeks. In contrast, the time spent in low FHR variation remains constant at about 28% (Dawes et al, 1982b). Episodes of high heart rate variation with clusters of fetal movement are present in over 99% of one hour recordings from 28 weeks onwards (Dawes et al, 1982b). FHR accelerations are usually associated with general movements (Dawes et al, 1981; Natale et al, 1985). In fetal sheep neuromuscular blockade with gallamine abolishes fetal movements but not the accelerations, which implies that accelerations cannot be due to fetal movements and suggests a central stimulus for body movements and increase of heart rate (Clewlow and Dawes, 1985). FHR accelerations are accompanied by arrest of fetal breathing and a decrease in beat-to-beat variation. Fetal breathing itself is associated with a small increase in beat-to-beat variation (Dawes et al, 1981).
Another behaviour variable is fetal eye movements. The eye can be visualized

ultrasonically in more than 90% of fetuses from 16 weeks postmenstrual age onwards (Birnholz, 1981). The fetal eyes are best displayed on an oblique cross-section of the fetal face. One or both eyes can be seen as a sonolucent globe, behind which lies a wedge-shaped echo-rich area (Bots et al, 1981). Improved resolution of present day real-time scanners allows a more detailed visualization of various components of the eye, such as the lens, iris, pupil, cornea and extraocular structures including muscles, retro-orbital fat and optic nerves (Birnholz, 1985). Limited ocular growth has been associated with delayed cerebral development (Birnholz, 1985).
Bots et al (1981) studying fetal eye movements in low risk pregnancies by means of combined real-time and M-mode ultrasonography, observed between 32 weeks and term either rapid or slow eye movements or a mixture of both types in 60 $\pm$ 10% (1SD) of 558 two minutes epochs. A detailed chronological study on the physiological development of fetal eye movements using the lens as a landmark was performed by Inoue et al (1986). They demonstrated that eye movements not only increase but begin to consolidate at about 24 weeks, after which this tendency becomes more distinct, resulting in long-term clusters of eye movement, particularly as from 30 weeks onwards.
With respect to the frequency of fetal eye movements, slow (low-frequency) eye movements ($<$ 10 per minute) can be seen as early as 16-18 weeks (Birnholz, 1981; Inoue et al, 1986), and much the same incidences are evident up to 37 weeks, although they do decrease sharply beyond 38 weeks (Inoue et al, 1986). Rapid (high-frequency) eye movements ($>$ 20 per minute) develop during the latter half of the second trimester (Birnholz, 1981; Inoue et al, 1986). As from 30-33 weeks there is a progressive expansion of the incidence of rapid eye movements and they are a major component of eye movements at term.

2.2 The emergence of fetal behavioural states

All above mentioned variables, i.e. fetal eye movements, fetal heart rate pattern, fetal motility and fetal heart rate changes associated with fetal motility, are closely related to the neurological condition of the fetus. Behavioural states in the newborn are temporarely stable conditions of neural and autonomic fluctuations such as sleep and wakefulness. A classification of behavioural states in the full term newborn was introduced by Prechtl and Beintema (1964) on easily observed state criteria, such as eyes open/closed; respiration regular/irregular; body movements present/absent. They recognized five states, namely:

State 1: eyes closed, no movements under the eyelids, regular respiration, no movements except sudden generalized startles.
State 2: eyes closed, eye movements under the closed eyelids, irregular respiration, small muscular twitches, no gross movements.
State 3: eyes open, no gross movements.
State 4: eyes open, movements of head, limbs and trunk.
State 5: crying or vocalisation

Attempts have been made to define states in the preterm infant (Parmelee, 1975; Stefanski et al, 1984). It appeared that the phenomenon of alignment between the state variables at the transition from one behavioural state to another develop

at around 36-38 weeks conceptial age in the preterm. Prior to this age, there is inconsistency in the fluctuation of the variables. It should be realized that periods of congruency of state variables may occur; however, they do not fit the behavioural state definition since they do not start and end simultaneously (Prechtl et al, 1979; Prechtl, 1985).

A search for the existence of behavioural states has also been made in the fetus both under animal experimental conditions and in man. In the near full term fetal lamb low voltage high frequency electrocortical activity was associated with the presence of irregular breathing and rapid eye movements (REM sleep), whereas high voltage low frequency electrocortical activity was observed in the presence of only isolated changes in intrathoracic pressure together with general fetal movements (NREM sleep) (Dawes et al, 1972). Also in the fetal rhesus monkey (Martin et al, 1974), evidence has been presented for the existence of two behavioural states: periods of quiescence characterized by a stable fetal heart rate and infrequent episodes of regular fetal breathing alternated with active periods of eye and body movements, increased fetal heart rate variation and frequent irregular breathing movements.

In the human fetus behavioural states were studied from fetal heart rate recordings alone (De Haan, 1979; Van Geyn et al, 1980), and in conjunction with body movements (Timor-Tritsch et al, 1978; Natale, 1985) resulting in the description of quiet and activity phases. The observations did not provide conclusive proof of the presence of true behavioural states in the human fetus since both fetal heart rate and fetal heart rate variability are affected by fetal motility (Wheeler and Guerard, 1974). Nijhuis et al (1982) stated that the presence of behavioural states can only be established following fulfillment of a number of criteria: a) particular conditions of several variables must recur in specific, fixed combinations; b) these combinations must be temporary stable; c) there should be clear state transitions. It was therefore necessary to study several independent variables with respect to the consistency and stability of their association and the simultaneity of their transition from one condition into another. Nijhuis et al (1982, 1984) clearly identified fetal behavioural states on the basis of eye and body movements and fetal heart rate patterns in low risk multigravidae as from 36-38 weeks of gestation. Four distinct behavioural states could be detected (state 1F to 4F), state 1F and 2F being most prevalent:

State 1F: quiescence, which can be regularly interrupted by brief gross body movements, mostly startles. Eye movements absent. Heart rate stable, with a small oscillation bandwidth (< 10 bpm). Isolated accelerations occur. These are strictly related to movements. This heart rate pattern is called FHRP-A.

State 2F: frequent and periodic gross body movements - mainly stretches and retroflexions - and movements of the extremities. Eye movements continually present (REMs and SEMs). Heart rate (called FHRP-B) with a wider oscillation bandwidth than FHRP-A (> 10 bpm) and frequent accelerations during movements.

State 3F: gross body movements absent. Eye movements continually present. Heart rate (called FHRP-C) stable, but with a wider oscillation bandwidth than FHRP-A and no accelerations.

State 4F: vigorous, continual activity including many trunk rotations. Eye movements continually present (when observable). Heart rate (called FHRP-D) unstable, with large and long-lasting accelerations, frequently fused into a sustained tachycardia.

At 38 weeks the distribution of percentages of stage 1F to 4F is respectively: 32%, 42%, 1% and 7% (Nijhuis et al, 1982).
Later studies (Van Vliet et al, 1985a; Arduini et al, 1985; 1986b) confirmed the presence of fetal behavioural states in the term fetus. Between 28 and 36 weeks the quiet-activity cycle of fetal heart rate was always detected and some fetal biophysical activities such as eye movements and micturition seem to become related around the cycles (Arduini et al, 1985). Van Vliet et al (1985a) were able to demonstrate that the development of behavioural states is generally similar in fetus of low risk nulliparas and multiparas, although states appear at somewhat later gestational age in the fetus of nulliparas.
The mechanism regulating fetal behaviour is still unknown. A relationship was observed between fetal behavioural changes and uterine contractions in pregnant sheep (Nathanielsz et al, 1980). Small falls in fetal oxygen level or fetal body compression have been suggested to be the mechanisms involved. However, it has been shown recently that neither Braxton-Hicks contractions (Mulder and Visser, 1987) nor uterine contractions as observed during labour (Hofmeyer et al, 1985) influence behavioural states in the human fetus. Of interest is the observation in the normal human fetus that both maternal triamcinolon administration inhibiting the fetal pituitary-adrenal axis (Arduini et al, 1986a) and maternal naloxone administration antagonizing the action of B-endorphin (Arduini et al, 1987) results in modification of fetal behavioural states with a prevalence of active sleep and active awake states compared to quiet sleep state. It was suggested that the mechanism of action could be the same.
The pituitary gland secretes adrenocorticotropic hormone and B-endorphin concomitantly, since both are derived from a common precursor, i.e. pro-opiomelanocortin (Mains et al, 1977). The location of the generator of fetal behavioural states is not known with certainty; some evidence points to the lower midbrain (Dawes, 1986). Administration of atropine to the fetal lamb causes prolonged high-voltage electrocortical activity while episodic fetal breathing movements continued (Van der Wildt, 1982; Bamford et al, 1985). The same effects were produced by hyoscine, but not by atropine metho-nitrate, which blocks the systemic muscarinic pathways but does not cross the blood-brain barrier (Bamford et al, 1985). It was concluded that administration of atropine interrupts a muscarinic pathway which runs from the hypothetical generator of fetal behavioural states and which normally, in the REM sleep rate, causes desynchronization of the local neuronal complex detected from the surface of the parietal cortex (Dawes, 1986).
Various investigators have undertaken to stimulate the fetus during periods of flat fetal heart rate tracing in an attempt to identify the sick fetus (Goodlin and Schmidt, 1972; Evertson and Paul, 1978; Paul and Keegan, 1979). No attention was paid to fetal behavioural states. Only recently, stimulation of the fetus was studied relative to the fetal behavioural state both in the fetal lamb (Natale and Nasello-Paterson, 1986) and in the human fetus (Visser et al, 1983; Schmidt et al, 1985; Ohel et al, 1986). A distinction should be made between

low variability and low activity of a healthy fetus in quiet sleep and a compromised fetus. It has been shown recently by Visser et al (1983) that shaking of the maternal abdomen does not contribute to this differentiation. In the human studies, in which acoustic stimulation was performed, Schmidt et al (1985) observed a fetal response characterized by increased fetal heart rate and motility, mainly during active sleep. A fetal response was also documented during quiet sleep by Ohel et al (1986).
In the fetal lamb study, during high voltage electrocortical activity without eye movements (quiet sleep), fetal response to brachial nerve stimulation was more pronounced than during low voltage electrocortical activity with eye movements (active sleep). It can be concluded that the behavioural state of the fetus before stimulation is an important determinant of observed responses in measurements of state variables such as fetal heart rate and fetal body movements.

2.3 Fetal behaviour and intrauterine growth retardation

Intrauterine growth retardation (IUGR) is usually defined on the basis of birthweight. The cut-off level for the diagnosis is either based on the 10th, 5th or 3rd percentile, or defined in terms of standard deviation, i.e. a birthweight equal to or less than -2 SD. Although the determinant of fetal growth is multifactorial, growth retardation in the fetus is generally considered the result of a relative oxygen deficiency or nutrition or both.
The effect of fetal hypoxia on the fetal behavioural state has been studied both in the fetal lamb and in the human fetus. In the fetal lamb, hypoxia causes suppression of breathing movements, fore limb movements and neck muscle activity. It also reduces the percentage of time that fetuses spent in low voltage electrocortical activity (Boddy et al, 1974; Natale et al, 1981; Martin et al, 1985; Bocking and Harding, 1986). No relationship could be demonstrated between this change in electrocortical activity and degree of acidosis (Bocking and Harding, 1986). The same investigations did however observe an inverse relationship between the gestational age of the fetus and the decrease in the incidence of low voltage electrocortical activity, i.e. older fetuses may be more resistent to the effect of hypoxia on electrocortical activity. It has been suggested that breathing movements and muscular activity are reduced during hypoxia as a means of decreasing oxygen requirements (Blanco et al, 1983; Dawes et al, 1983). Breathing movements are associated with an increase in fetal oxygen consumption of 17% to 30% (Rurack and Gruber, 1983a and b). According to Bocking and Harding however, it seems unlikely that the decrease in the percentage of time that the fetus spends in low-voltage electrocortical activity is an attempt by the fetus to conserve oxygen during reduced supply, since cerebral metabolic rate remains constant despite a decrease in arterial pO_2 to 14 mm Hg (Jones et al, 1977).
Furthermore, there was no significant difference in overall fetal oxygen consumption between episodes of low-voltage and high-voltage electrocortical activity (Walker et al, 1984).
In the growth-retarded human fetus state transitions are generally poorly synchronized and do not display any apparent improvement in synchrony of transitions with gestational age (Van Vliet et al, 1985b). It was suggested that

this relative absence of synchronized state transitions may reflect disfunction of the central nervous system as a result of metabolic disturbance or delayed maturation.

2.4 Fetal behavioural states and blood flow

Little information is available on fetal blood flow relative to fetal behavioural states. Nearly all available data originate from chronic lamb preparations. Clapp et al (1980) measured a significant increase in mean arterial pressure and umbilical blood flow during low-voltage electrocortical activity. In contrast Zhu and Szeto (1987) were unable to demonstrate significant electrocortical activity-related changes in fetal mean arterial pressure. During the low voltage electrocortical state cerebral blood flow is raised (Richardson et al, 1985; Jensen et al, 1985b). This rise particularly occurs in the subcortex and pons, close to the reticular formation. Richardson et al (1985) point out that this may reflect a close coupling of blood flow to neuronal activity, which is known to be variously increased in these structures during the low-voltage electrocortical state (Siegel, 1979; Greenberg, 1980).
A decrease in blood flow during low-voltage activity was measured in the wall of the ductus arteriosus, possibly suggesting constriction in this state of activity (Jensen et al, 1985b). It was suggested that this constriction of the ductus arteriosus during low-voltage activity may represent a mechanism causing preferential streaming of oxygenated blood to the heart and brain. The low-voltage electrocortical activity is not only associated with an increase in blood flow to the brain stem areas, but also with increased flow to the gastrointestinal tract and in the pancreas (Jensen et al, 1985b). Only very limited information is available from human studies.
In a recent study by Mulders et al (1986) it is demonstrated that in normal term pregnancy, the blood flow velocity waveform in the umbilical artery shows no state dependency.
In the asymmetrically growth-retarded human fetus between 36-38 weeks of gestation a delay in integration of behavioural patterns and lower coincidence of behavioural states was particularly observed in the absence of end-diastolic blood flow in the fetal descending aorta (Rizzo et al, 1987). It was suggested that there is a possible relationship between this delay and the degree of peripheral vascular resistance.

Chapter 3

FETAL BEHAVIOURAL STATES AND BLOOD FLOW IN THE FETAL DESCENDING AORTA

Introductory remarks

The articles presented in this chapter describe characteristic changes which occur in the blood flow velocity waveforms in the lower thoracic part of the fetal descending aorta relative to fetal behavioural states. Emphasis has been put on behavioural states 1F (quiet sleep) and 2F (active sleep) according to Nijhuis et al (1982). The incidence of behavioural states 3F and 4F was too low to obtain reliable blood flow velocity waveforms. Measurements were carried-out in normal pregnancy and in intrauterine growth retardation at 37-38 weeks (3.1 and 3.2) and in normal pregnancy at 27-28 weeks of gestation (3.3).

3.1 The blood flow velocity waveform in the fetal descending aorta; its relationship to fetal behavioural states in normal pregnancy at 37-38 weeks of gestation

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Modified version.

Summary

In 13 normal pregnancies, the relationship between the blood flow velocity waveform at the lower thoracic level of the fetal descending aorta and fetal behavioural states at 37-38 weeks of gestation was studied. The pulsatility index (PI), as a measure of peripheral vascular resistance, was significantly lower during state 2F compared to state 1F according to the classification by Nijhuis et al (1982), suggesting an increased perfusion of the fetal skeletal musculature to meet the energy demand needed for the raised muscular activity during state 2F. A significant inverse relationship ($p < 0.001$) was established between PI and FHR, which was mainly determined by a significant rise in end-diastolic flow velocity ($p < 0.02$).
Both the behavioural state and FHR should be taken into account when evaluating flow velocity waveforms in the fetal descending aorta during the latter weeks of pregnancy.

Introduction

With the introduction of combined real-time and pulsed Doppler ultrasound systems a non-invasive method of studying fetal blood flow has become available (Eik-Nes et al, 1980; Griffin et al, 1983; Tonge et al, 1983). However, errors that arise in assessing vessel diameter and fetal weight by ultrasound have resulted in attention turning to qualitative interpretation of blood flow velocity waveforms. Normal values for the various components of the flow velocity waveform in the lower thoracic part of the fetal descending aorta have been established in the third trimester of pregnancy by various centres (Jouppila et al, 1984; Marsal et al, 1984; Tonge et al, 1984b). Recently, clear evidence was provided for the existence of behavioural states in the human fetus from 37-38 weeks onwards (Nijhuis et al, 1982). Based on the marked changes in fetal heart rate pattern and incidence of fetal body movements between different behavioural states, it is not unlikely that these changes are associated with alterations in fetal cardiovascular performance. The objective of the present study was to establish a possible relationship between the flow velocity waveform in the fetal descending aorta and fetal behavioural state, in particular state 1F and 2F according to the classification of Nijhuis et al (1982).

Material and methods

A total of 13 non-smoking patients with normal singleton pregnancies at 37-38 weeks of gestation gave consent to participate in the study. The gestational age had been calculated from a reliable menstrual history and early ultrasonic measurement of fetal crown-rump length or biparietal diameter. The deliveries were uneventful. Fetal birthweight was between the 10th and 90th percentile for gestational age according to Kloosterman's Tables corrected for maternal parity and fetal sex (Kloosterman, 1970). No medications were prescribed. All patients were studied in the semi-recumbent position. Recordings were started 2 h after a meal and had to last at least one hour. Using a combined real-time scanner and pulsed Doppler system as described by Eik-Nes et al (1980), the mean blood flow velocity at the lower thoracic level of the fetal descending aorta was recorded. The Doppler probe (Pedoff) was attached to the linear array real-time transducer so that the Doppler beam intersected the fetal descending aorta at a fixed angle of 45°. The beam direction with the sample gate position (electronic marker) could be displayed on the real-time screen. The flow velocity waveform in an artery is governed by the cardiac contraction force, compliance of the vessel wall, blood viscosity and peripheral resistance (MacDonald, 1974). The end-diastolic position of the waveform is an important index of peripheral resistance. The blood flow velocity waveform was recorded during fetal apnoea, over a 5-second period which included on average 10 consecutive cardiac cycles. In each flow velocity recording at least 7 optimal cardiac cycles were selected and the mean value for the peak velocity (PV, cm/sec), end-diastolic velocity (EDV, cm/sec), averaged velocity (AV, cm/sec) and instantaneous fetal heart rate (FHR) were calculated (Fig. 1). A frequently used index to characterize the pulsatility of fetal arterial flow velocity waveforms is the Pulsatility Index

(PI) which is defined using the following formula (Gosling et al, 1975):

$$PI = \frac{PV - EDV}{AV}$$

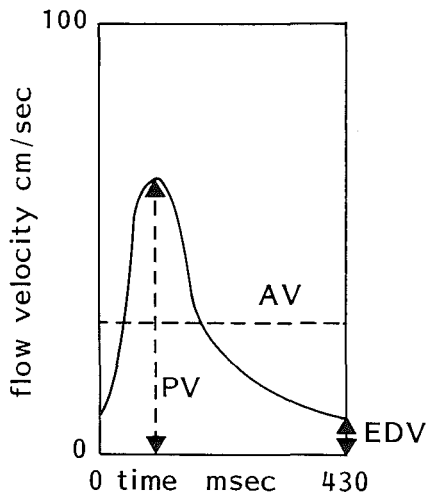

Figure 1. Flow velocity profile at the lower thoracic level of the fetal descending aorta at 37-38 weeks of gestation. PV = peak velocity (cm /sec); EDV = end-diastolic velocity (cm /sec); AV = averaged velocity (cm /sec).

Blood flow velocity waveform recordings in the lower thoracic part of the fetal descending aorta were carried-out during fetal behavioural state 1F and 2F as described by Nijhuis et al (1982). These behavioural states were defined as follows:

State 1F: quiescence, which can be regularly interrupted by brief gross body movements that mostly are startles; absent eye movements and a stable heart rate pattern with a small oscillation bandwidth. Isolated accelerations do occur, but these are strictly related to movements.

State 2F: frequent and periodic gross body movements that are mainly stretches and retroflexions and movements of extremities; eye movements continuous and a heart rate pattern with a wider oscillation bandwidth than in state 1F and frequent accelerations during movements.

State 3F and 4F were excluded because of the low incidence of these behavioural states, respectively 1% and 7% (Nijhuis et al, 1982). Moreover during 4F the fetus moves continuously too vigorous to obtain reliable blood flow velocity waveforms.

In order to establish these fetal behavioural states, the following parameters were recorded:

a. The fetal heart rate (FHR), which was obtained from a Doppler Ultrasound Cardiotocograph (Hewlett Packard 8040 A).
b. Fetal eye movements which were studied from a transverse view of the fetal face using a 2-dimensional real-time linear array scanner (Toshiba Sal 20 A).

c. Fetal body movements from a second 2-dimensional real-time linear array scanner (Organon Teknika Cardiovisor 03) for a sagittal view of the fetal trunk.

Figure 2 gives a schematic design of the way the study was performed.

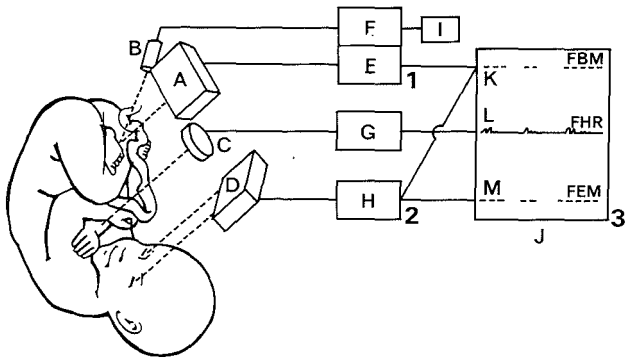

Figure 2. Schematic design of the way a recording was performed.

A real time linear array scanner (fetal body movements)
B pulsed Doppler system fixed to A under an angle of 45°
C fetal heart rate transducer
D real time linear array scanner (fetal eye and head movements)
E Organon Teknika Cardiovisor 03
F Pedoff (pulsed Doppler)
G Hewlett Packard 8040 A cardiotocograph
H Toshiba Sal 20 A
I Apple III microcomputer for analysis of the flow velocity data
J 3-channel writer
K input fetal body movements (head, trunk, extremities)
L input fetal heart rate pattern
M input fetal eye movements
1 person 1 who registrates fetal body movements and performs flow velocity measurements
2 person 2 who registrates fetal eye- and head movements
3 person 3 who identifies fetal behavioural states and gives the signal to start flow velocity measurements

Each flow velocity recording was preceded by a fetal behavioural state determination over a period of at least 3 minutes (Nijhuis et al, 1982). In each patient a minimum of 5 flow velocity recordings in state 1F and 2F was obtained. The analysis of the data was as follows:

In each patient and for each fetal behavioural state, the flow velocity data were divided into groups, each of which represented a FHR range of 5 bpm. This division was introduced in order to standardize cardiac output, since at normal heart rates the fetal myocardium seems to operate near the plateau of the Starling function curve (Kirkpatrick et al, 1976; Tonge et al, 1984b), e.g. cardiac output is regulated through changes in FHR. Changes in the flow velocity waveform will now predominantly reflect changes in peripheral vascular resistance. Within each FHR range the mean value (± 1SD) for all 4 flow velocity parameters

in state 1F and 2F was calculated. Changes in mean flow velocity values with respect to the fetal behavioural state and FHR were tested using the paired Student's t test.

Results

The mean number of cardiac cycles studied for all 13 patients was 55 (min: 26; max: 101) in state 1F and 58 (min: 26; max: 95) in state 2F, a total of 1480 cycles. FHR in state 1F ranged between 103 and 171 bpm and in state 2F between 94 and 185 bpm.
Paired flow velocity data in state 1F and 2F were observed in the FHR range between 106 and 165 bpm. Statistical analysis of the paired differences was feasible in the FHR range between 121 and 150 bpm, resulting in 6 groups e.g. 121-125, 126-130,....., 146-150 bpm in a total number of 1320 cardiac cycles. Table I represents for each flow velocity parameter in each of the fetal behavioural states,the lowest and highest mean value (± 1SD). Table II shows the statistical significance of the paired differences in PI, EDV, PV and AV between state 1F and 2F per FHR range. A lower PI and higher EDV was observed in state 2F as compared with state 1F. PV and AV demonstrated no statistical significant difference between state 1F and 2F in most FHR ranges studied.

Table I. Lowest and highest mean values (± 1SD) for the pulsatility index (PI), peak velocity (PV), end-diastolic velocity (EDV) and averaged velocity (AV) at the lower thoracic level of the fetal descending aorta in relation to fetal behavioural state and FHR.

Flow velocity waveform parameters	Fetal behavioural state	$\overline{X}$ max	SD	FHR range (bpm)	$\overline{X}$ min	SD	FHR range (bpm)
PI	1F	2.7	0.3	106-110	2.1	0.1	161-165
	2F	2.2	0.3	106-110	1.8	0.1	161-165
PV (cm /sec)	1F	88.9	7.2	106-110	77.4	8.9	151-155
	2F	81.5	8.9	106-110	75.7	4.8	161-165
EDV (cm /sec)	1F	11.8	1.8	161-165	7.1	2.1	116-120
	2F	14.1	1.3	161-165	9.7	3.3	121-125
AV (cm /sec)	1F	33.1	8.0	161-165	28.3	3.6	116-120
	2F	35.4	3.2	156-160	30.2	3.6	121-125

$\overline{X}$ max and $\overline{X}$ min = highest and lowest mean value.

A significant reduction ($p < 0.001$) in PI with increasing FHR was established, which was mainly determined by a significant rise ($p < 0.02$) in EDV.
Figure 3 depicts for each FHR the mean PI in state 1F and 2F for all 1480 cardiac cycles studied (93-185 bpm). An inverse linear relationship between PI and FHR in both behavioural states was established with a regression equation in state 2F: PI = -0.0052 × FHR + 2.693 (SD slope ± 0.0008) and in state 1F: PI = -0.0116 × FHR + 3.978 (SD slope ± 0.0009).

Table II. Statistical significance (paired Student's t test) of the paired differences in pulsatility (ΔPI), end-diastolic velocity (ΔEDV), peak velocity (ΔPV) and averaged velocity (ΔAV) per FHR-range.

FHR range (bpm)	n	Δ PI 1F-2F	SD	P	Δ PI 2F-1F	EDV SD	P	Δ PV 1F-2F	PV SD	P	Δ AV 2F-1F	AV SD	P
121-125	8	0.43	0.21	<0.001	2.70	2.78	<0.05	7.36	4.75	<0.01	1.06	1.82	<0.20*
126-130	9	0.36	0.17	<0.001	2.66	1.53	<0.001	3.41	6.09	<0.20*	1.99	1.76	<0.01
131-135	10	0.35	0.18	<0.001	2.98	2.40	<0.01	4.80	8.07	<0.20*	1.26	2.78	<0.20*
136-140	9	0.33	0.21	<0.002	4.48	3.05	<0.01	2.47	2.32	<0.02	2.04	2.66	<0.10*
141-145	10	0.38	0.24	<0.001	5.01	2.21	<0.001	2.00	6.22	>0.20*	2.57	3.07	<0.05
146-150	6	0.26	0.19	<0.05	3.05	2.49	<0.05	3.44	7.92	>0.20*	1.05	2.89	>0.20*

n = number of paired observations per FHR-range.
* = statistically not significant

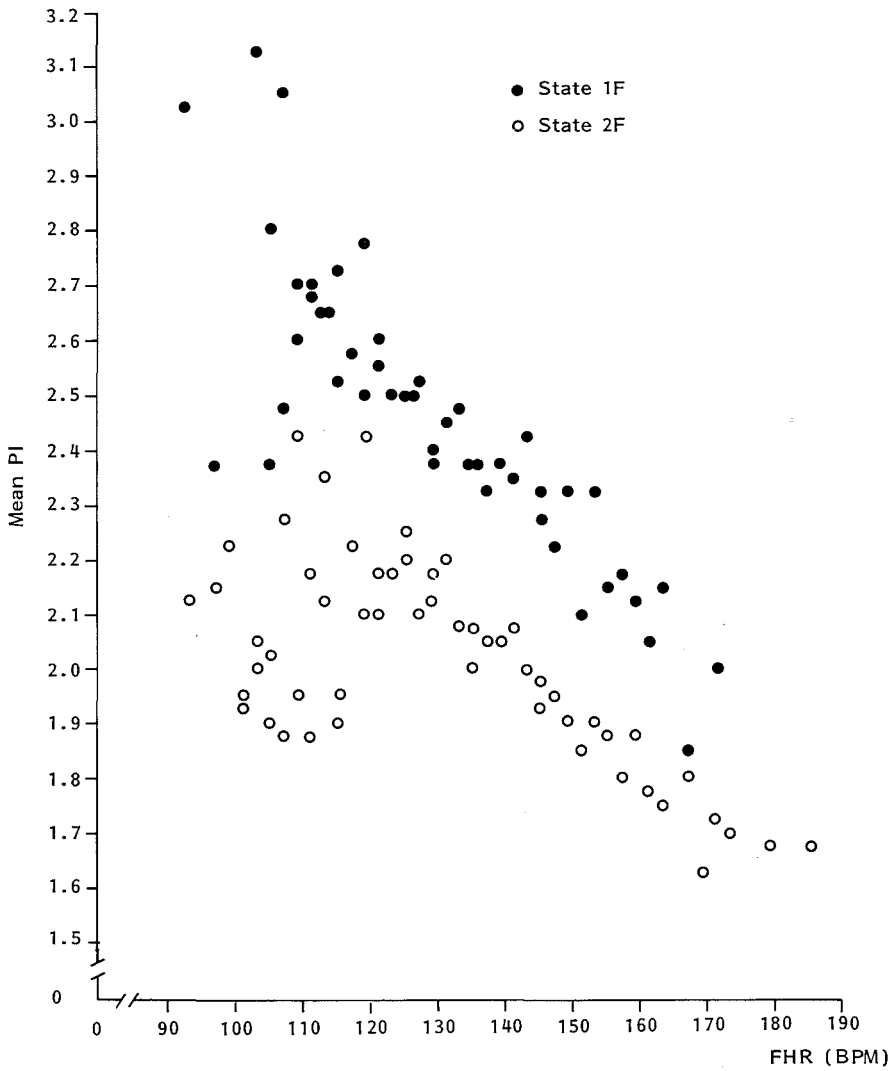

Figure 3. The mean pulsatility index of the flow velocity profile for each FHR at the lower thoracic level of the fetal descending aorta relative to FHR in all cardiac cycles studied.

Discussion

Since real-time ultrasound has opened the possibility for studying various aspects of fetal dynamics, a considerable amount of information has been gathered on fetal central nervous and cardiovacular development.
Non-invasive Doppler measurements of blood flow in the fetal descending aorta and umbilical vein have shown that fetal blood flow is modulated by fetal breathing movements (Marsal et al, 1984b). The marked difference in PI between behavioural state 1F and 2F observed in our study is nearly entirely determined by changes in end-diastolic blood flow velocity. The reduced PI and elevated EDV in the fetal descending aorta reflect reduced fetal peripheral vascular resistance, suggesting an increased perfusion of the fetal skeletal musculature (trunk and lower extremities). Due to the increased muscular activity in behavioural state 2F there is a raised energy demand. The fetal origin of the state dependent PI and EDV changes is supported by preliminary data from umbilical artery velocity waveforms in which no such state dependency was observed. The above-mentioned changes in peripheral vascular resistance in relation to fetal behavioural states poses the interesting question as to what extent a fetus under less favourable circumstances such as in placental insufficiency is still capable of this vascular adaptation. This is particularly important in the light of reduced end-diastolic blood flow velocities in the fetal descending aorta observed during intrauterine growth retardation (Griffin et al, 1984; Jouppila et al, 1984).
The inverse relationship between PI and FHR both in state 1F and 2F reflects a gradual reduction in peripheral vascular resistance with increasing FHR. This is most likely determined by the gradual increase in the incidence of fetal body movements in relation to rising fetal heart rate, particularly in state 2F. The wide distribution of mean PI values at low heart rates between 100 and 115 bpm especially in state 2F (Fig. 3) is mainly determined by the relatively low PI values from one individual patient.
Both the fetal behavioural state and FHR dependency of the PI in the descending aorta of the term fetus are of practical significance when evaluating flow velocity waveforms in this vessel. This applies particularly to the analysis of EDV in the early detection of intrauterine growth retardation. It can therefore be concluded that fetal behavioural state and heart rate should be taken into account when studying flow velocity waveforms in the fetal descending aorta.

3.2 The blood flow velocity waveform in the fetal descending aorta; its relationship to behavioural states in the growth-retarded fetus at 37-38 weeks of gestation

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Summary

In 12 patients with intrauterine growth retardation (IUGR), the relationship between the blood flow velocity waveform at the lower thoracic level of the fetal descending aorta and fetal behavioural states at 37-38 weeks of gestation was studied. A significant inverse relationship ($p < 0.001$) was established between pulsatility index (PI) and fetal heart rate (FHR) in state 1F and 2F. The PI as a measure of peripheral vascular resistance, demonstrated a marked increase compared to normal pregnancy. There is a virtual overlap of PI values originating from state 1F and 2F according to the classification by Nijhuis et al (J.G. Nijhuis, H.F.R. Prechtl, C.B. Martin, Jr. and R.S.G.M. Bots (1982) Early Hum. Dev. 6, 177-195). The peripheral vasoconstriction present in IUGR seems to overrule state dependent PI fluctuations. The marked rise in PI, particularly at lower FHR and the constancy of PI in relation to fetal behavioural states can be considered vascular adaptations, which are instrumental in the centralization of the fetal circulation, with the aim of favouring blood supply to the brain, heart and adrenals during IUGR.

fetus; blood flow velocity; aorta descendens; behavioural state; fetal growth retardation

Introduction

Combined use of real-time and pulsed Doppler systems has now resulted in a large number of studies on fetal blood flow (Eik-Nes et al, 1980; Griffin et al 1983; Tonge et al, 1983). Whereas, initial work dealt mainly with volume flow measurements, the relatively large errors associated with the estimation of vessel size soon resulted in attention turning to the qualitative analysis of blood flow velocity waveforms (Griffin et al, 1984; Marsal et al, 1984b).
A number of reports have been published recently, in which IUGR was associated with an increased fetal-placental peripheral vascular resistance, resulting in a rise in PI in the fetal descending aorta and umbilical artery (Jouppila et al, 1984, Reuwer et al, 1984). In an earlier study (Van Eyck et al, 1985) we were able to demonstrate in the normal term fetus a marked reduction in PI in the flow velocity waveform originating from the lower thoracic part of the descending

aorta during behavioural state 2F as compared with behavioural state 1F according to the classification by Nijhuis et al (1982). This finding suggests an increased perfusion of the fetal skeletal musculature to meet the energy demand during raised muscular activity in behavioural state 2F. The question arises as to whether in the presence of a raised peripheral vascular resistance, as is observed in IUGR, the fetus is still capable of this vascular adaptation.
The objective of the present study was, therefore, to establish as to whether in IUGR state dependent changes in PI at the lower thoracic level of the fetal descending aorta are similar to those observed in normal pregnancy.

Subjects and Methods

A total of 12 patients with IUGR at 37-38 weeks of gestation gave consent to participate in the study. The gestational age had been calculated from a reliable menstrual history and early ultrasonic measurements of fetal crown-rump length or biparietal diameter.
IUGR was defined as follows:

a. a progressive asymmetric slow-down in increase of fetal head and upper abdominal circumference resulting in values below the 5th percentile of the nomograms by Campbell and Wilkin (1975);
b. fetal birth weight below the 5th percentile for gestational age according to Kloosterman's tables, corrections being made for maternal parity and fetal sex (Kloosterman, 1970).

Maternal blood pressure was raised (> 140 /90 mm Hg) in six out of 12 patients. There was no serological evidence of fetal infection. There were no signs of fetal distress during the behavioural studies. Eleven out of twelve infants were delivered vaginally. One was delivered by caesarian section because of suspected fetal distress. There were no congenital abnormalities. The Apgar score at 5 min was nine or higher.
All patients were studied in the semi-recumbent position. Recordings were started 2 h following a meal and had to last at least one hour. A combined real-time scanner and pulsed Doppler system similar to that described in our previous study (Van Eyck et al, 1985) was used. The mean blood flow velocity waveform at the lower level of the fetal descending aorta was recorded during fetal apnoea over a 5 s period which included on average 10 consecutive cardiac cycles.
In each flow velocity recording at least seven optimal cardiac cycles were selected and the mean value for the peak velocity (PV), end-diastolic velocity (EDV) and averaged velocity (AV) as well as the instantaneous fetal heart rate (FHR) was established. From the velocity data the PI as defined by Gosling and King was calculated (Gosling et al, 1975).
Blood flow velocity waveform recordings in the lower part of the fetal descending aorta were carried out during fetal behavioural state 1F and 2F as described by Nijhuis et al (1982). The incidence of behavioural state 3F and 4F was too low to obtain reliable blood flow velocity waveforms. In order to establish these fetal behavioural states, the following parameters were recorded simultaneously:

a. the FHR, which was obtained from a Doppler ultrasound cardiotocograph (Hewlett-Packard 8040 A);

b. fetal eye movements which were studied from a transverse view of the fetal face using a two-dimensional real-time linear array scanner (Toshiba SAL 20A);
c. fetal body movements from a second two-dimensional real-time linear array scanner (Organon Teknika, cardiovisor 03) from a sagittal view of the fetal trunk.

We found a stable combination of these three state variables with short transitions within 3 min. Our patients therefore displayed true fetal behavioural states and not only coincidence of the variables. Flow velocity recordings were only performed when the state had been stable for at least 3 min. In each patient a minimum of five flow velocity recordings in each behavioural state (1F and 2F) was obtained. At normal heart rates, the fetal myocardium seems to operate near the plateau of the Starling function curve, e.g. cardiac output is mainly regulated through changes in FHR (Kirkpatrick et al, 1976; Marsal et al, 1982; Rudolph, 1985). It was therefore decided to standardize cardiac output which was carried out as follows: in each patient and for each fetal behavioural state, the flow velocity data were divided into groups, each of which represented a FHR range of five beats per minute (BPM). Flow velocity waveform changes will now predominantly reflect changes in peripheral vascular resistance. For all four flow velocity parameters (PV, EDV, AV and PI), the mean value (± 1SD) in each FHR range was calculated both in state 1F and 2F. Changes in mean flow velocity values with respect to the fetal behavioural state and FHR were tested using the 95% confidence limit. The relationship between PI and FHR was tested by analysing the slopes of the individual regression lines, using Student's t-test.

Results

The averaged duration of fetal behavioural state recordings was 70.0 ± 8.4 (1SD) min. The percentage of time in which there was coincidence of all three parameters was 84.8 ± 6.8 (1SD)%. The percentage of time spent in state 1F was 35.8 ± 7.5 (1SD)% and in state 2F 49.0 ± 8.8 (1SD)%. The time spent in state 1F was relatively high because the recording was stopped when sufficient flow velocity data in both states were obtained. The mean number of cardiac cycles studied for all 12 patients was 81 (min. 32; max. 127) in state 1F and 86 (min. 52; max. 153) in state 2F, a total of 2004 cycles. FHR in state 1F ranged between 111 and 169 BPM and in state 2F between 115 and 176 BPM. Paired analysis of the flow velocity data in state 1F and 2F was statistically feasible in the FHR range between 121 and 165 BPM resulting in 9 groups, e.g. 121-125, 126-130, ... 161-165 BPM in a total of 1888 cardiac cycles. The 95% confidence interval of the paired difference in mean PI between state 1F and 2F (Table I) displays for each FHR range a narrow distribution around zero, reflecting a virtual overlap of PI values originating from state 1F and 2F. This also accounts for the components of the PI, e.g. EDV, PV and AV as shown in Table I and Fig. 1. Using Student's t-test a significant reduction ($p < 0.001$) in PI with increasing FHR was established in both state 1F and 2F. This was mainly determined by a rise in AV, which was significant in state 1F ($p < 0.05$). No significant change in PV and EDV was observed. Figure

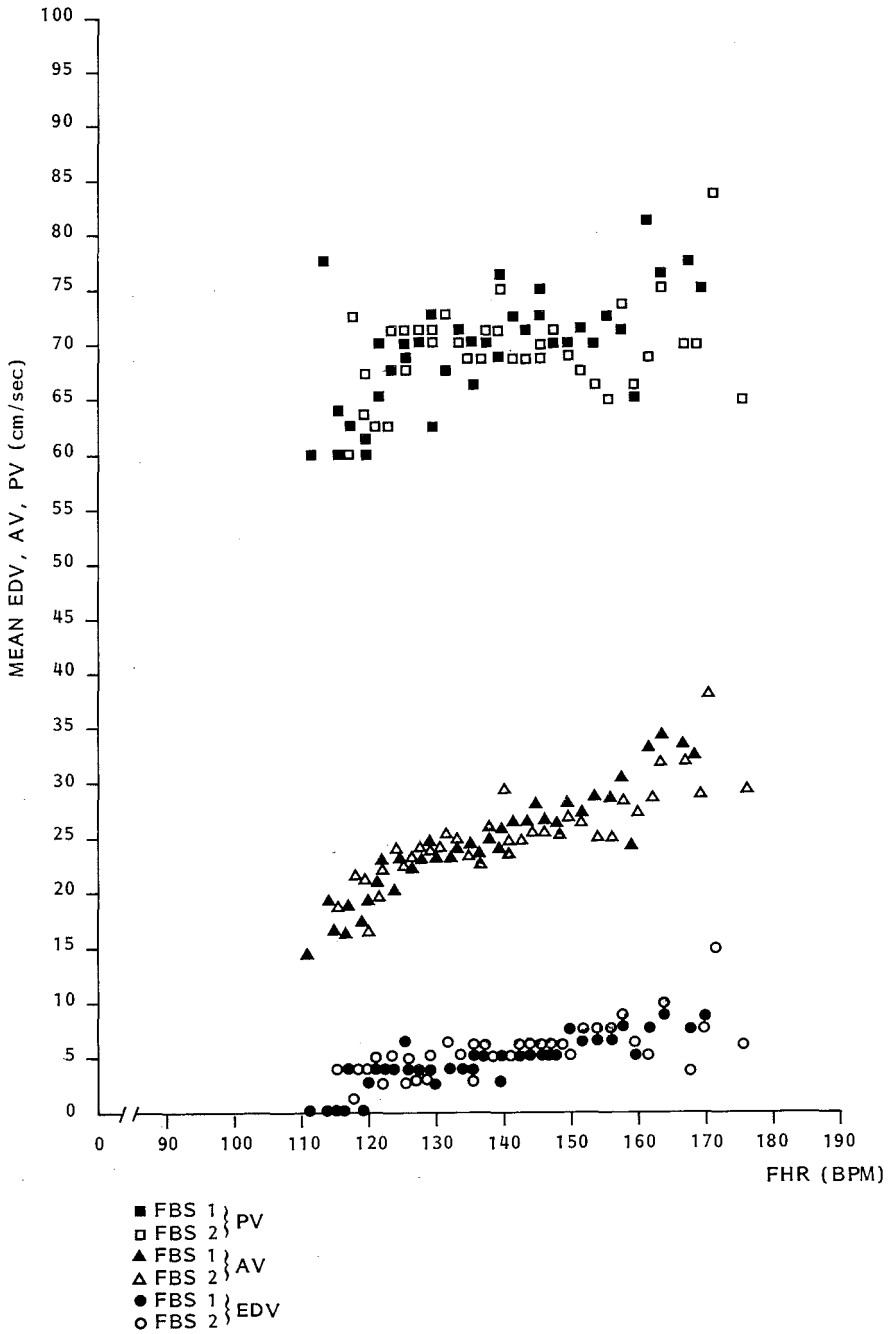

Figure 1. Mean EDV, AV and PV (cm /s) in state 1F (FBS 1) and state 2F (FBS2) relative to FHR.

Table I. The 95% confidence interval of the paired difference in mean PI, EDV, AV and PV between state 1F and 2F for each of the FHR ranges studied.

FHR range	Mean PI 1F minus mean PI 2F	95% Confidence interval			
		PI	EDV (cm/s)	AV (cm/s)	PV (cm/s)
121-125	0.02	-0.14, +0.18	-1.99, +0.81	-0.88, +1.68	-3.60, +3.60
126-130	0.01	-0.12, +0.14	-1.20, +1.54	-2.14, +2.06	-6.50, +5.14
131-135	0.09	-0.02, +0.22	-1.51, +2.07	-1.49, +1.23	-4.95, +3.05
136-140	0.02	-0.11, +0.03	-1.41, +0.77	-2.42, +1.12	-5.68, +3.96
141-145	-0.05	-0.01, +0.11	-0.40, +1.22	-1.97, +0.39	-6.54, +0.68
146-150	0.00	-0.08, +0.10	-1.17, +1.15	-1.85, +1.21	-6.66, +3.62
151-155	0.04	-0.06, +0.12	-1.01, +0.83	-2.28, +1.02	-6.77, +0.43
156-160	-0.04	-0.15, +0.09	-2.28, +1.70	-3.53, +3.67	-8.62, +7.42
161-165	0.01	-0.01, +0.03	-8.86, +5.90	-2.77, +2.21	-20.33, +15.11

2 demonstrates for each FHR the mean PI in state 1F and 2F for all 2004 cardiac cycles studied (111-176 BPM). An inverse relationship between PI and FHR in both behavioural states was established with a regression equation in state 2F: $PI = -0.0218 \times FHR + 5.745$ (SD slope $\pm$ 0.001) and in state 1F: $PI = -0.0302 \times FHR + 7.003$ (SD slope $\pm$ 0.002). In Fig. 3 all PI values of the present study are plotted together with the PI values from a normal population reported in a previous study (Van Eyck et al, 1985). Note the markedly elevated PI levels in IUGR, particularly at lower heart rates, and their virtual overlap when relating these values to state 1F and 2F.

Discussion

All fetuses in our study displayed growth retardation expressed by asymmetric slow-down in increase of fetal head and upper abdominal circumference. There were no congenital defects or signs of intrauterine infection. Although fetal birth weight was always below the 5th percentile, there was no evidence of fetal distress at the time of the behavioural observations. Fetal behavioural states are characterised by coincidence of all three parameters and short transitions from one state to another (Nijhuis et al, 1982). Recently Van Vliet et al (1985a) established that clear fetal behavioural states appear 2 weeks later in nulliparous women compared to multiparous women. Van Vliet et al also demonstrated that at a comparable gestational age, the appearance of fetal behavioural states as described by Nijhuis et al (1982) is delayed in asymmetrical growth retardation as compared with low risk pregnancies (Van Vliet, 1985a). Especially there was a reduced percentage of brief transitions. It should be realised, however, that of the 12 patients with IUGR studied by Van Vliet et al only seven were seen at 37-38 wk of gestation, five of which were nulliparous women (71%). In our IUGR population, however, 75% of the patients had one or more previous pregnancies. In all growth-retarded fetuses of the present study, both state 1F and 2F were recorded over a sufficient period of time to ensure an acceptable number of fetal aortic blood flow velocity recordings.

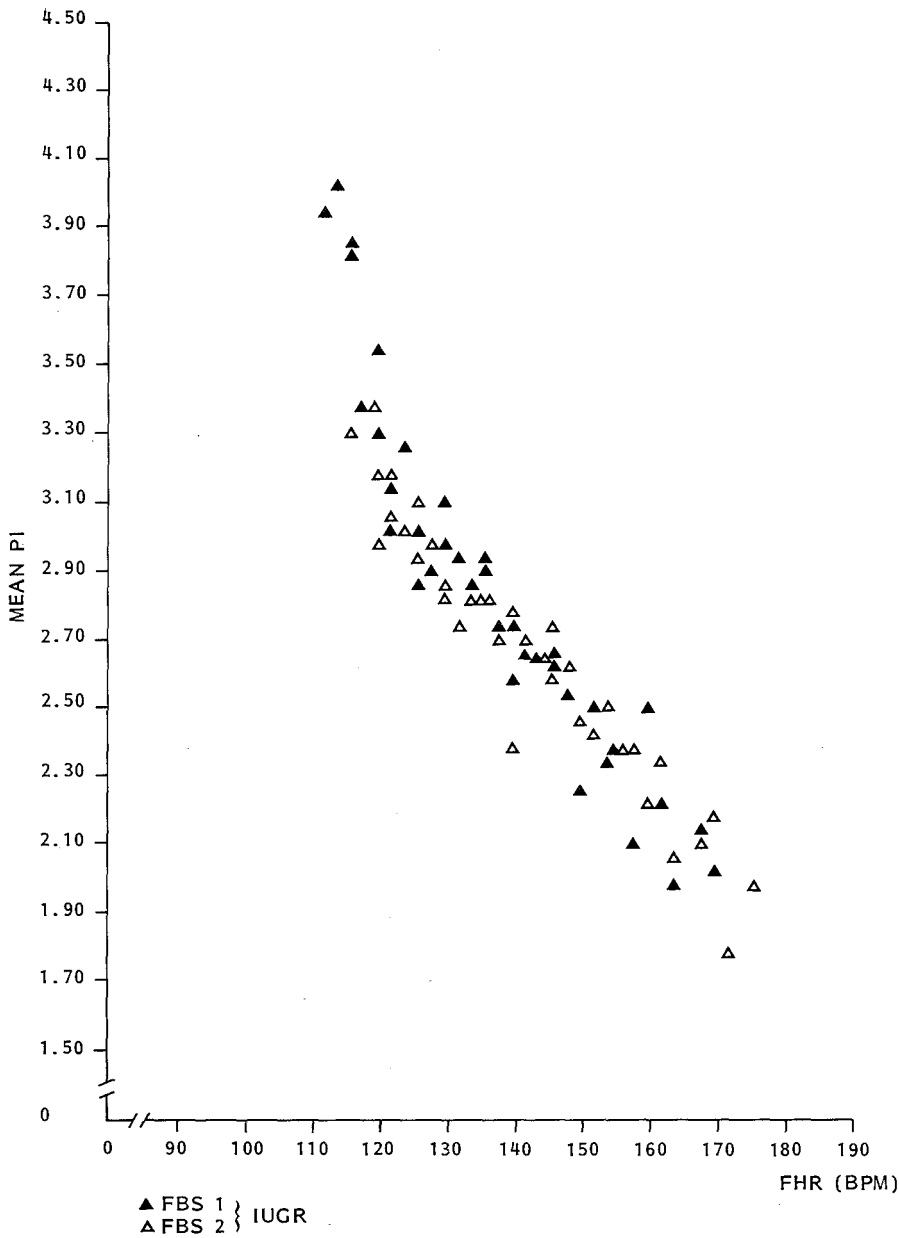

Figure 2. Mean PI in state 1F (FBS 1) and state 2F (FBS 2) relative to FHR.

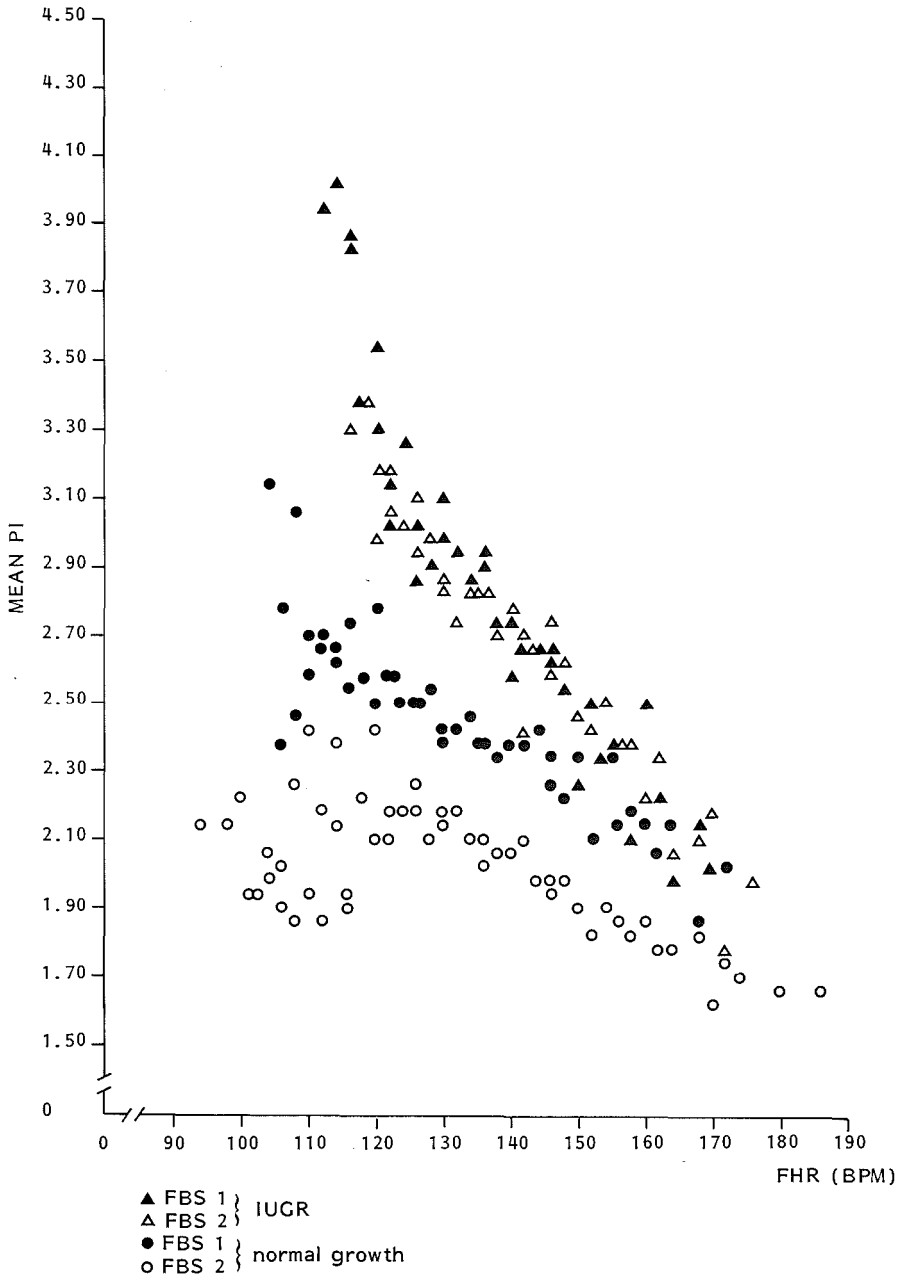

Figure 3. Mean PI in state 1F and 2F in IUGR (present study) and in normal growth (Van Eyck et al, 1985) relative to FHR.

In IUGR PI and FHR showed an inverse linear relationship which was even more pronounced than in normal growth.
This inverse linear relationship between PI and FHR is partly due to the way PI is calculated. The marked rise in PI in the fetal descending aorta reflects increased peripheral vascular resistance in presence of IUGR, as has also been reported by others (Griffin et al, 1984; Jouppila et al, 1984; Tonge et al, 1986b). Whereas in the normal fetus (Van Eyck et al, 1985) increased peripheral perfusion documented by a reduction in PI and rise in EDV was established in state 2F, this change did not occur in IUGR. This may be explained by the fact that chronic hypoxia present in IUGR stimulates the peripheral arterial chemoreceptors (Critchley et al, 1980; Dawes et al, 1968a; Itskoviz et al, 1982) and subsequent release of vasoconstrictive agents, such as vasopressin and catecholamines (Iwamoto et al, 1979; Iwamoto et al, 1981; Jensen et al, 1982; Mott, 1985; Oosterbaan, 1985). This peripheral vasoconstriction seems to overrule state dependent PI fluctuations. Consequently the increased energy demand, needed for raised muscular activity during state 2F, may not be adequately met.
All above mentioned observations, i.e. the marked rise in PI, particularly at lower FHR and the constancy of PI in relation to fetal behavioural states can be considered vascular adaptations, which are instrumental in the centralization of the fetal circulation favouring blood supply to the brain, heart and adrenals during IUGR (Jensen et al, 1985a; Oosterbaan, 1985; Pohjavuori et al, 1980; Pohjavuori et al, 1983). In the light of these findings the administration of tocolytic agents such as betamimetics during IUGR seems questionable (Vetter et al, 1985).
Recently Doppler ultrasound studies have demonstrated that in the asymmetrically growth retarded human fetus, the PI is reduced in the internal carotid artery suggesting a compensatory reduction in peripheral vascular resistance in the fetal cerebrum, i.e. a brain-sparing effect in the presence of fetal hypoxia (Wladimiroff et al, 1986). Based on this observation, it would be of interest to know if fetal behavioural states are also associated with changes in carotid blood flow velocity waveforms.
Finally, the present data emphasize once more the importance of determining both fetal behavioural state and FHR when studying flow velocity waveforms in the fetal descending aorta for clinical purposes.

3.3 The blood flow velocity waveform in the fetal descending aorta; its relationship to fetal heart rate pattern, eye and body movements in normal pregnancy at 27-28 weeks of gestation

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Summary

In 13 normal pregnancies at 27-28 weeks of gestation the blood flow velocity waveform at the lower thoracic level of the fetal descending aorta was studied in relation to fetal heart rate pattern (FHRP), fetal eye movements (FEM) and fetal body movements (FBM).
State parameter combinations in which high fetal heart rate (FHR) variability was present, were associated with a significant reduction in Pulsatility Index (PI) as compared with periods in which low FHR variability was present, irrespective of FEM and FBM, indicating a reduced peripheral vascular resistance. At 27-28 weeks of gestation FHR variability and PI might be linked to baroreceptor sensitivity. PI values derived from combinations FHRP-A, FEM (-), FBM (-) and FHRP-B, FEM (+), FBM (+) showed a significant inverse relationship ($p < 0.05$) with FHR.
FHR and FHR variability should be taken into account when studying flow velocity waveforms in the fetal descending aorta at 27-28 weeks of gestation.

Key words: Fetal blood flow velocity waveform; fetal descending aorta; behavioural state variables.

Introduction

Recently, a clear relationship was demonstrated between fetal behavioural states (Nijhuis et al, 1982) and Pulsatility Index (PI) values in the fetal descending aorta and internal carotid artery in normal term pregnancies (Van Eyck et al, 1985, 1987). In both vessels PI was significantly reduced in state 2F as compared with state 1F, indicating a reduced peripheral vascular resistance. The question arises as to whether one of the state variables, i.e. fetal heart rate pattern (FHRP), eye movements (FEM) or body movements (FBM) is particularly associated with these PI changes. Since from 36 weeks onwards these state variables show alignement with short transition periods from combined presence to combined absence of these variables and vice versa, it is not possible to perform this analysis in the fetus at term. At 27-28 weeks of gestation there are episodes of low and high heart rate variability (FHR-A and FHR-B pattern), with and without eye movements (FEM) and body movements (FBM). There is no proper

synchronization in the cyclic appearance of these variables. Periods of coincidence occur often by chance and will result in the occurrence of eight combinations of state parameters. The objective of the present study was therefore to investigate the relationship between these single state parameters and the PI in the fetal descending aorta at 27-28 weeks of gestation.

Subjects and Methods

A total of 13 healthy subjects with normal singleton pregnancies at 27-28 weeks of gestation gave consent to participate in the study. Gestational age had been calculated from a reliable menstrual history and early ultrasonic measurement of fetal crown-rump length or biparietal diameter. All subjects were non-smokers, no medications were prescribed. All pregnancies were uneventful, resulting in the delivery at term of a healthy infant with a birthweight between the 50th and 95th percentile for gestational age according to Kloosterman's Tables, corrected for maternal parity and fetal sex (Kloosterman, 1970). All studies were carried out two hours following breakfast or lunch with the subject in the semi-recumbent position. Each study had to last at least one hour.

Using a combined real-time scanner and pulsed Doppler system as described by Eik-Nes et al (1980), the mean blood flow velocity at the lower thoracic level of the fetal descending aorta was recorded. The Doppler probe (Pedoff, carrier frequency 2 MHz) was attached to the linear array real-time transducer so that the Doppler beam intersected the fetal descending aorta at a fixed angle of 45°. The beam direction with the sample gate position (electronic marker) could be displayed on the real-time screen. The blood flow velocity waveform was recorded during fetal apnoea, over a five second period which included on average 10 consecutive cardiac cycles. In each flow velocity recording at least seven optimal flow velocity waveforms were selected.

State variables were recorded simultaneously:

a. The fetal heart rate (FHR), which was obtained from a Doppler ultrasound Cardiotocograph (Hewlett Packard 8040 A, carrier frequency 1 MHz); FHR was classified as pattern A (FHRP-A) and B (FHRP-B).
   The first pattern is characterized by a stable heart rate with an oscillation bandwidth of < 10 bpm (low variability). The latter pattern is characterized by an oscillation bandwidth of > 10 bpm (high variability).
b. Fetal eye movements (FEM), which were studied from a transverse view of the fetal face using a mechanical sector scanner (Diasonics CV 400; carrier frequency 3.5 MHz). As in previous studies FEM were identified from the lens and considered present when at least one lens movement per minute was observed.
c. Fetal body movements (FBM)), which were obtained from a sagittal view of the fetal trunk, using a real-time linear array scanner (Organon Teknika, Cardiovisor 03, carrier frequency 3.2 MHz). The three transducers were placed in such a way, that there was minimal interference between the three ultrasound modes. Only the absence or presence of FBM was established without differentiation into the type of movement.

Blood flow velocity recordings were performed when a stable combination of the three state parameters had been present over a period of at least three minutes.

The maximum amount of time allowed between the completion of a stable state variable determination and the completion of a flow velocity recording was three minutes. Using a microcomputer the instantaneous FHR and PI was calculated, the latter according to the method of Gosling and King (1975).
PI changes predominantly reflect changes in peripheral vascular resistance (Noordam et al, 1987). Since at normal fetal heart rates, changes in cardiac output are mainly regulated through changes in FHR (Kirkpatrick et al, 1976; Marsal et al, 1984b) it was decided to standardize cardiac output by dividing the PI values in each subject and for each state parameter combination into groups, each of which representing a FHR range of 5 bpm. This standardization will also rule out the effect created by the dependency of the PI on the length of the cardiac cycle when comparing PI values between the various state parameter combinations.
The data analysis was carried out in two steps:
First, all PI values obtained from epochs with combined presence (code 111) or absence (code 000) of FHRP-B, FEM and FBM were compared (Table I).

Table I. Mean duration for each state parameter combination as percentage of time.

STATE VARIABLE COMBINATIONS				Code	TIME %	TIME SD
1.	FHRP-A	FEM-	FBM-	000	15.4	6.1
2.	FHRP-A	FEM-	FBM+	001	7.6	5.7
3.	FHRP-A	FEM+	FBM-	010	1.9	3.2
4.	FHRP-A	FEM+	FBM+	011	3.9	6.8
5.	FHRP-B	FEM-	FBM-	100	8.6	7.2
6.	FHRP-B	FEM-	FBM+	101	33.4	10.0
7.	FHRP-B	FEM+	FBM-	110	1.3	2.1
8.	FHRP-B	FEM+	FBM+	111	27.9	10.0

Analysis of the mean PI differences per FHR range of 5 bpm was performed using the paired Student's t-test. The relationship between PI and FHR was tested by analysing the slopes of the individual regression lines using the Student's t-test.
Second, the relationship between individual state variables and PI was studied. Analysis of the relationship with FHRP consisted of comparison of the following four pairs of coincidences of state parameters (Table I): 000-100, 001-101, 010-110 and 011-111. In this way flow velocity waveforms were obtained from epochs, in which FHRP was the only variable in combination with the same FEM and FBM distribution. Analysis of the relationship with FEM consisted of comparison of 000-010, 001-011, 100-110 and 101-111; analysis of the relationship with FBM led to the comparison of 000-001, 010-111, 100-101 and 110-111. Again the PI data were standardized for FHR and divided into groups of 5 bpm each. Analysis of the mean PI differences per FHR range of 5 bpm was performed using the paired Student's t-test when at least five or more paired observations per FHR range were obtained.

Results

The mean duration of a recording was 69.5 ± 9.5 min., which may be considered sufficient for completion of a quiet-active cycle (Visser et al, 1981).
Table I shows that episodes of low FHR variation (FHRP-A) were observed in 28.8% and episodes of high FHR variation were observed in 71.2% of the total recording time.
The mean number of cardiac cycles studied in the fetal descending aorta for each subject during epochs with the state variable combination FHRP-A, FEM (-), FBM (-) was 27 (min. 7; max. 57) and with the state variable combination FHRP-B, FEM (+), FBM (+) was 28 (min. 8; max. 64), a total of 722 cardiac cycles.
Paired analysis of the PI data for both combinations was feasible in the FHR range between 136-160 bpm, resulting in 5 groups i.e. 136-140, 141-145, ... 156-160 bpm, a total of 458 cardiac cycles.
There is a statistically significant reduction in mean PI in the presence of state parameter combination FHRP-B, FEM (+), FBM (+) as compared with the coincidence of FHRP-A, FEM (-), FBM (-) (Table II). A statistically significant inverse relationship between PI and FHR was established in both combinations ($p < 0.05$).

Table II. Mean paired PI difference (PI ± 1SD) per FHR range between combined absence (code 000) and presence (code 111) of FHRP-B, FEM and FBM in the fetal descending aorta.

FHR range (bpm)	Number of paired observations	Mean PI for code 000	Mean PI for code 111	ΔPI	SD	Statistical significance	
136-140	8	2.47	1.99	0.48	0.22	$p < 0.001$	S
141-145	9	2.39	1.96	0.43	0.44	$p < 0.02$	S
146-150	7	2.32	1.84	0.48	0.18	$p < 0.001$	S
151-155	7	2.33	1.95	0.38	0.31	$p < 0.02$	S
156-160	6	2.35	2.03	0.32	0.18	$p < 0.01$	S

S = significant.

The mean PI differences (PI ± 1SD) per FHR range between state variable combinations in which FHRP-A or FHRP-B is present, is depicted in Table III. Paired analysis was feasible between the combinations 011-111 and 001-101, in a total of 255 cardiac cycles.
A statistically significant reduction in mean PI is demonstrated in the presence of FHRP-B as compared with FHRP-A. In the combinations 010-110 and 000-100 the number of paired observations was too small to allow statistical analysis.
In Table IV the mean PI difference (PI ± 1SD) per FHR range between state variable combinations in which FEM are absent or present is shown. Paired analysis was feasible between the combinations 101-111 and 000-010, in a total of 528 cardiac cycles. There is no statistically significant change in mean PI relative to the absence or presence of FEM. In the combinations 100-110 and 001-011 statistical analysis was not feasible. There is no statistically significant change in mean PI relative to the absence or presence of FBM as

Table III. Mean paired PI difference (PI ± 1SD) per FHR range between state parameter combinations in which FHRP-A or FHRP-B is present.

FHR range (bpm)	Number of paired observations	Mean PI for code 011	Mean PI for code 111	ΔPI	SD	Statistical significance
146-150	5	2.36	1.91	0.45	0.29	$p < 0.02$ S
151-155	5	2.49	1.97	0.52	0.33	$p < 0.02$ S
156-160	5	2.39	1.95	0.44	0.29	$p < 0.02$ S
		for code 001	for code 101			
146-150	5	2.43	2.05	0.38	0.16	$p < 0.01$ S

For coding see Table I. S = significant.

Table IV. Mean paired PI difference (PI ± 1SD) per FHR range between state parameter combinations in which FEM are absent or present.

FHR range (bpm)	Number of paired observations	Mean PI for code 101	Mean PI for code 111	ΔPI	SD	Statistical significance
131-135	5	2.33	2.29	0.04	0.37	$p > 0.2$ NS
136-140	10	2.11	1.97	0.14	0.33	$p > 0.2$ NS
141-145	8	2.12	1.91	0.21	0.25	$p < 0.1$ NS
146-150	7	2.11	2.01	0.10	0.28	$p > 0.2$ NS
151-155	6	2.11	2.00	0.11	0.37	$p > 0.2$ NS
156-160	5	2.02	2.13	-0.11	0.40	$p > 0.2$ NS
		for code 000	for code 010			
146-150	5	2.61	2.40	0.21	0.22	$p < 0.1$ NS

For coding see Table I. NS = not significant.

can be seen in Table V. Paired analysis was feasible in the combinations 000-001 and 100-101, in a total of 233 cardiac cycles. In the combinations 110-111 and 010-011 the number of paired observations was not sufficient to allow statistical analysis.

Table V. Mean paired PI difference (PI ± 1SD) per FHR range between state parameter combinations in which FBM are absent or present.

FHR range (bpm)	Number of paired observations	Mean PI for code 000	Mean PI for code 001	ΔPI	SD	Statistical significance
141-145	6	2.42	2.32	0.10	0.35	$p > 0.2$ NS
146-150	6	2.51	2.39	0.12	0.17	$p < 0.2$ NS
151-155	5	2.33	2.20	0.13	0.45	$p > 0.2$ NS
		for code 100	for code 101			
136-140	5	1.92	2.02	-0.10	0.15	$p > 0.2$ NS

For coding see Table I. NS = not significant.

Discussion

The present data are in agreement with the existence of fetal rest-activity cycles (Sterman et al, 1971) and their relationship with low and high heart rate variation as early as 27-28 weeks of gestation (Visser et al, 1981; Dawes et al, 1982a).
The distribution of FHRP-A and FHRP-B demonstrates a predominance of the latter pattern, i.e. 71.2% of the total recording time, which is close to that (80.4%) observed by Arduini et al (1986b). Fetal body movements are clearly present during episodes with FHRP-B at this time of pregnancy (61.3%) as has also been pointed out in previous studies (Dawes et al, 1982a; Sorokin et al, 1982; Natale et al, 1985).
Following the introduction of fetal eye movement studies using real-time ultrasound (Bots et al, 1981) and the recognition of various types of eye movements with their characteristic sequence of development (Birnholz, 1981), it was Nijhuis et al (1982) who investigated the biological implications of these movements relative to fetal behavioural states. Both from the present study and data by Inoue et al (1986), the percentage incidence of eye movements at 27-28 weeks of gestation seems to vary between 35 and 45%.
In the present study only a change in PI relative to the FHR pattern was established. In chronically instrumented fetal lambs it was demonstrated that arterial baroreceptors are important in regulating variability of the arterial pressure and heart rate in fetal life, and also may play a significant role in maintaining the normal peripheral vascular resistance (Shinebourne et al, 1972; Itskovitz et al, 1983). Differences in sensitivity of the baroreflex during different behavioural states were demonstrated in fetal lambs (Zhu and Szeto, 1987) and cats (Baccelli et al, 1976). In fetal sheep an increased baroreceptor sensitivity was observed during high voltage electrocortical activity (Zhu and Szeto, 1987). As the FHR pattern is one of the state variables, it could well be that this state variable is related to baroreceptor sensitivity. The assumption that the human fetus exhibits increased baroreceptor sensitivity during episodes of high FHR variability would explain the observation in the present study that PI changes in the fetal descending aorta are related to the FHR variability, i.e. reduced PI in the presence of FHRP-B.

In earlier studies a relationship between PI and fetal behavioural states was demonstrated in the human fetus at term (Van Eyck et al, 1985, 1987). It might well be that at term PI is also related to only one state variable, i.e. FHRP and not to the others. Similar to term pregnancy (Van Eyck, 1985, 1987) an inverse relationship between FHR and PI was observed. Both FHR and FHR variability should therefore be taken into account when studying flow velocity waveforms in the fetal descending aorta at 27-28 weeks of gestation.

Chapter 4

FETAL BEHAVIOURAL STATES AND BLOOD FLOW IN THE FETAL INTERNAL CAROTID AND UMBILICAL ARTERY

Introductory remarks

Recently, a pulsed Doppler method was introduced for recording the flow velocity waveform in the internal carotid artery in the human fetus (Wladimiroff et al, 1986). From this study it appeared that in the growth retarded fetus the Pulsatility Index (PI) was reduced in the internal carotid artery, suggesting a compensatory reduction in peripheral vascular resistance in the fetal cerebrum i.e. a brain-sparing effect in the presence of fetal hypoxia.
The first two articles (4.1 and 4.2) deal with a cross-sectional (37-38 weeks) and a longitudinal study (36-41 weeks) of fetal internal carotid blood flow velocity waveforms relative to fetal behavioural states 1F and 2F. The cross-sectional study also includes blood flow velocity waveforms in the umbilical artery.
In the last two articles (4.3 and 4.4) blood flow velocity waveforms in the internal carotid and umbilical artery are studied in growth-retarded fetuses in general and relative to fetal behavioural states 1F and 2F.

4.1 The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relationship to fetal behavioural states in normal pregnancy at 37-38 weeks of gestation

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Modified version.

Summary

The relationship between the blood flow velocity waveform in the fetal internal carotid artery (n = 12) and umbilical artery (n = 15) and fetal behavioural states at 37-38 weeks of gestation was studied. In the fetal internal carotid artery, under standardized fetal heart rate conditions, the Pulsatility Index (PI)

as a measure of peripheral vascular resistance, was significantly lower during behavioural state 2F compared to state 1F according to the classification by Nijhuis et al (1982), suggesting increased fetal cerebral blood flow during state 2F. In the umbilical artery, no significant difference in PI between the two behavioural states could be established. This suggests a fetal origin of the state dependency observed in fetal blood flow velocity waveforms.

Introduction

Recently it has been demonstrated in the normal developing human fetus in late pregnancy that fetal behavioural states affect blood flow velocity waveforms in the lower thoracic part of the descending aorta. Using the classification of Nijhuis et al (1982), the Pulsatility Index was significantly reduced during behavioural state 2F (active sleep) compared to behavioural state 1F (quiet sleep) (van Eyck et al, 1985). It was suggested that these changes may reflect an increased perfusion of the skeletal musculature during behavioural state 2F.
Recently, a Doppler ultrasound method for recording the blood flow velocity waveform in the fetal internal carotid artery was developed (Wladimiroff et al, 1986). The question arises, as to whether the state dependency of fetal aortic blood flow also exists for the fetal internal carotid artery and umbilical artery. This may be of clinical importance since flow velocity waveforms in both vessels are now being increasingly studied relative to the detection of intrauterine growth retardation (Giles, 1982; Schulman et al, 1984; Reuwer et al, 1984; Trudinger et al, 1985; Wladimiroff et al, 1986, 1987a).
If a fetal regulatory mechanism is responsible for the observed state dependent changes in the fetal descending aorta, then state dependent changes could also be expected in the fetal internal carotid artery with state independency in the umbilical artery.
The objective of the present study was to establish the relationship between the blood flow velocity waveform in the fetal internal carotid and umbilical artery and fetal behavioural states, in particular state 1F and 2F during normal term pregnancy.

Subjects and Methods

A total of 15 normal subjects with singleton pregnancies at 37-38 weeks of gestation consented to participate in the study. The gestational age had been calculated from a reliable menstrual history and early ultrasonic measurement of fetal crown-rump length or biparietal diameter. Fetal birth weight was between the 25th and 90th percentile for gestational age according to Kloosterman's Tables corrected for maternal parity and fetal sex (Kloosterman, 1970). All subjects were non-smokers, no medications were prescribed. All studies were carried out two hours following breakfast or lunch, with the subject in the semi-recumbent position.
A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400) was used in 15 subjects for recording the maximum flow velocity waveform in the umbilical artery and fetal internal carotid artery at the level

of the bifurcation into the middle and anterior cerebral artery (Fig. 1) (Wladimiroff et al, 1986). Only recordings depicting simultaneous arterial and venous flow velocity patterns were accepted as originating from the umbilical cord. Venous blood flow had to be constant to ensure fetal apnoea was present.

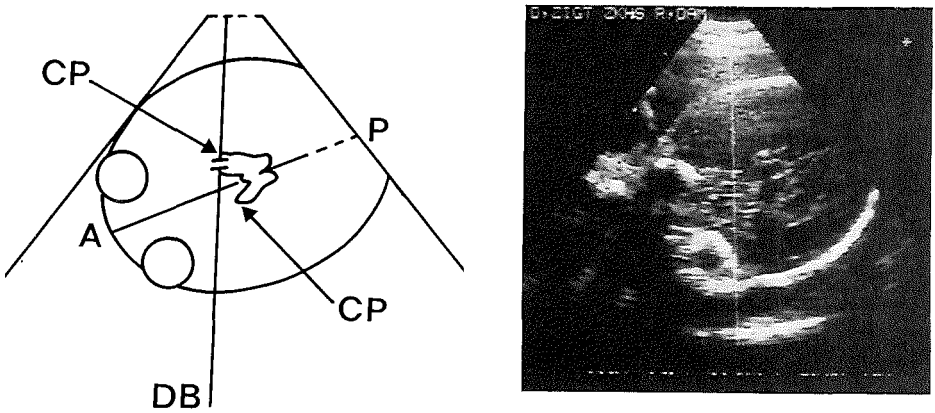

Figure 1. Ultrasonic cross-section and schematic representation of the fetal head at the level of the bifurcation of the fetal internal carotid artery into the middle and anterior cerebral artery.

Maximum flow velocity waveforms were recorded during fetal behavioural states 1F and 2F according to Nijhuis et al (1982). These behavioural states are defined as follows:

State 1F: quiescence which can be regularly interrupted by brief gross body movements which mostly are startles; absent eye movements and a stable heart pattern with a small oscillation bandwidth. Isolated accelerations do occur, but these are strictly related to movements.

State 2F: frequent and periodic gross body movements that are mainly stretches and retroflexions and movements of extremities; eye movements continuous and a heart rate pattern with a wider oscillation bandwidth than in state 1F and frequent accelerations during movements.

The incidence of behavioural states 3F and 4F is too low to obtain enough blood flow velocity waveforms. Moreover in behavioural state 4F the fetus moves continuously too vigorous to perform reliable blood flow velocity measurements. In order to establish fetal behavioural states, the following parameters were simultaneously recorded:

a. The fetal heart rate (FHR), which was obtained from a Doppler ultrasound Cardiotocograph (Hewlett Packard 8040A, carrier frequency 1 MHz);
b. Fetal eye movements which were studied from a transverse view of the fetal face using the Diasonics CV 400 (carrier frequency 3.5 MHz);
c. Fetal body movements from a 2-dimensional real-time linear array scanner (Toshiba Sal 20A, carrier frequency 3.5 MHz) for a sagittal view of the fetal trunk.

The three transducers were placed in such way, that there was minimal interference between the three ultrasound modes.
Flow velocity recordings were only performed when a clear fetal behavioural state was identified and when this state had been present over a period of at least three minutes. All recordings were performed during fetal apnoea. The maximum amount of time for the completion of a flow velocity recording following a state determination was three minutes.
The blood flow velocity waveforms were recorded on videotape over a 15-second period which included an average of 30 consecutive cardiac cycles. In each subject a minimum of three flow velocity waveform recordings in each vessel in each behavioural state (1F and 2F) was obtained. From hard copies of each flow velocity recording on average 20 cardiac cycles of optimal quality were selected. The degree of pulsatility of the waveform was quantified by calculating the Pulsatility Index (PI) according to Gosling and King (1975) using a microcomputer (Apple III). The PI changes predominantly reflect changes in peripheral vascular resistance. Since at normal fetal heart rates, changes in cardiac output are mainly regulated through changes in FHR (Kirckpatrick et al, 1976; Marsal et al, 1984b), it was decided to standardize cardiac output by dividing the PI values in each subject and for each fetal behavioural state into groups, each of which representing a FHR range of 5 bpm. This standardization will also rule out the effect of cardiac cycle length dependency of the PI when comparing PI values between behavioural states 1F and 2F. Changes in PI values with respect to the fetal behavioural state were tested using the paired Student's t-test. The relationship between PI and FHR was tested by analysing the slopes of the individual regression lines using the Student's t-test.

Results

In three subjects the blood flow velocity recordings in the fetal internal carotid artery in either behavioural state 1F or 2F had to be rejected due to poor quality or was not obtained at all as a result of hiccups, fetal breathing or excessive body movements or deep engagement of the fetal head. The mean number of cardiac cycles studied in the fetal internal carotid artery for all 12 subjects was 56 (min. 47; max. 68) in state 1F and 59 (min. 26; max. 76) in state 2F, a total of 1381 cycles. FHR in state 1F ranged between 109 and 164 bpm and in state 2F between 109 and 185 bpm. Paired analysis of the PI data in state 1F and 2F was feasible in the FHR range between 121 and 145 bpm resulting in five groups i.e. 121-125, 126-130, ..., 141-145 bpm in a total number of 1021 cardiac cycles.
There is a statistically significant difference in mean PI between state 1F and 2F for all of the FHR ranges studied (Table I). Figure 2 demonstrates the regression lines for the correlation between PI and FHR in state 1F (continuous lines) and 2F (dotted lines) for all 12 subjects. A significant reduction in PI with increasing FHR was established in state 1F ($p < 0.005$) and 2F ($p < 0.001$).
The mean number of cardiac cycles studied in the umbilical artery for all 15 subjects was 59 (min. 38; max. 82) in state 1F and 58 (min. 33; max. 76) in state 2F, a total of 1752 cycles. FHR in state 1F ranged between 105 and 185 bpm and in state 2F between 102 and 188 bpm. Paired analysis of the

Table I. Mean paired PI difference (ΔPI ± 1SD) between fetal behavioural states 1F and 2F in the FHR range between 121 and 145 bpm in the fetal internal carotid artery for normal pregnancy.

FHR range (bpm)	Number of paired observations	Mean PI State 1F	State 2F	ΔPI	SD	Significance
121-125	8	1.58	1.20	0.38	0.13	$p < 0.001$
126-130	10	1.59	1.23	0.36	0.16	$p < 0.001$
131-135	9	1.49	1.18	0.31	0.16	$p < 0.001$
136-140	10	1.60	1.24	0.36	0.21	$p < 0.001$
141-145	8	1.54	1.19	0.35	0.18	$p < 0.001$

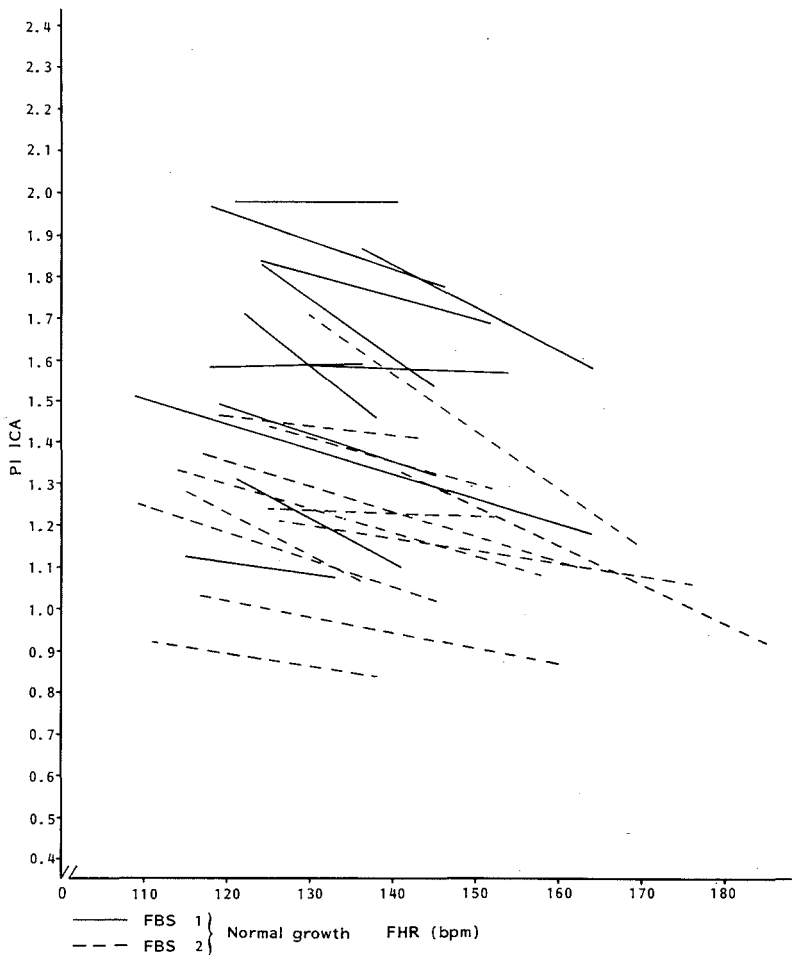

Figure 2. Regression lines for the correlation between PI and FHR in fetal behavioural state 1F (continuous lines) and 2F (dotted lines) in the fetal internal carotid artery for all 12 normal pregnancies.

flow velocity data in state 1F and 2F was statistically feasible in the FHR range between 121 and 150 bpm resulting in six groups i.e. 121-125, 126-130, ..., 146-150 bpm in a total of 1449 cardiac cycles. Table II shows a non-significant paired difference in mean PI between states 1F and 2F. Moreover, the 95% confidence interval of this paired difference displays for each FHR range a narrow distribution around zero, reflecting a virtual overlap of PI values originating from states 1F and 2F. Figure 3 demonstrates for each FHR the mean PI in states 1F and 2F for all 15 subjects studied (102-188 bpm). An inverse relationship between PI and FHR both in behavioural state 1F ($p < 0.05$) and 2F ($p < 0.001$) was established.

Table II. Mean paired PI difference ($\Delta PI \pm 1SD$) and 95% confidence interval between fetal behavioural states 1F and 2F in the FHR range between 121 and 150 bpm in the umbilical artery for normal pregnancy.

FHR range (bpm)	Number of paired observations	Mean PI State 1F	Mean PI State 2F	ΔPI	SD	Significance	95% confidence Interval
121-125	9	0.83	0.83	0.00	0.05	$p > 0.20$ (NS)	-0.04,0.04
126-130	12	0.84	0.80	0.04	0.08	$p > 0.10$ (NS)	-0.01,0.09
131-135	14	0.84	0.82	0.02	0.11	$p > 0.20$ (NS)	-0.04,0.08
136-140	11	0.80	0.79	0.01	0.09	$p > 0.20$ (NS)	-0.05,0.07
141-145	11	0.79	0.76	0.03	0.10	$p > 0.20$ (NS)	-0.04,0.10
146-150	7	0.83	0.77	0.06	0.09	$p > 0.10$ (NS)	-0.02,0.14

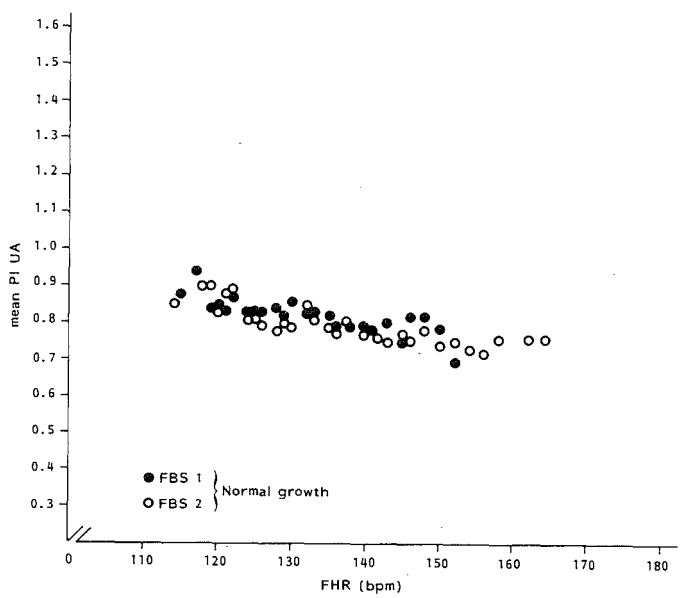

Figure 3. Mean PI in the umbilical artery in fetal behavioural states 1F (FBS1) and 2F (FBS2) relative to FHR for all 15 normal pregnancies.

Discussion

Both in the fetal lamb and in the human fetus cycling of behavioural parameters into identifiable states has become apparent over the last few weeks of pregnancy. Sleep state has been shown to influence cerebral blood flow in animals (Reivich et al, 1968), human neonates (Mukhtar et al, 1982) and adult man (Townsend et al, 1973), i.e. an increase has been documented during rapid eye movement sleep (active sleep) when compared to non-rapid eye movement sleep (quiet sleep). Combined 2-dimensional real-time and pulsed Doppler systems allow non-invasive recording of flow velocity waveforms in the human fetal internal carotid artery. However, due to its winding path into the skull only angle-independent measurements can be made. The decrease in PI in the internal carotid artery during behavioural state 2F as demonstrated in our study, suggests a reduction in peripheral vascular resistance in the fetal brain. Comparison of cerebral blood flow as measured by microspheres and pulsed Doppler in young piglets (Hansen et al, 1983) and newborn lambs (Rosenberg et al, 1985), demonstrated that peak systolic and end-diastolic velocity as well as the area under the velocity curve, reflecting the shape of the waveform closely correlate with cerebral blood flow. Since the Pulsatility Index is determined by all these three variables, the observed reduction in this index in the human fetal internal carotid artery under standardized FHR conditions during behavioural state 2F suggests an increase in cerebral blood flow during this state.

Of interest is the observation in fetal lamb that there is a significant increase in cerebral oxidative metabolism during the low-voltage electrocortical state (active sleep) (Richardson et al, 1985) which is sustained by a rise in cerebral blood flow, which is most pronounced in the subcortex and brain stem areas (Jensen et al, 1985b; Richardson et al, 1985). The question as to whether a similar pattern of flow distribution is present in the human fetus may be answered by studying the flow velocity waveforms in the internal carotid artery and vertebro-basilar circulation, the latter being mainly responsible for the blood supply to the brain stem areas. Preliminary data from our Unit have demonstrated that in these two cerebral vessels, reproducible flow velocity waveforms can be obtained. The possible clinical importance of flow velocity waveform recordings in the human fetal internal carotid artery is mainly based on a reduction in peripheral vascular resistance in the fetal cerebrum i.e. a brain-sparing effect in intrauterine growth retardation (Wladimiroff et al, 1986, 1987a).

Whereas in normal pregnancies and under standardized FHR conditions, the Pulsatility Index in the lower thoracic part of the fetal descending aorta (van Eyck et al, 1985) and fetal internal carotid artery depicts significant changes with respect to the fetal behavioural state, this is not so for the umbilical artery. This fetal behavioural state independency suggests a fetal regulatory mechanism for the state dependent changes in the fetal descending aorta and internal carotid artery. The state independency in the umbilical artery is of practical importance, since in contrast to the above-mentioned fetal vessels, flow velocity waveform studies in the umbilical artery during the latter weeks of pregnancy can be carried-out without taking the fetal behavioural state into account.

The decrease in PI with rising fetal heart rate observed in both the fetal internal carotid artery and umbilical artery has also been established in the fetal descending aorta both in normal and growth retarded pregnancies (van Eyck et al, 1985,

1986). This inverse relationship is mainly determined by the definition presented by Gosling and King (1975) for PI calculations, i.e. at a lower FHR a more gradual end-diastolic slow-down of the blood flow velocity takes place. It is essential, therefore, that when studying the effect of behavioural state on fetal blood flow, PI calculations are standardized for fetal heart rate.
It can be concluded from the presented data that under standardized FHR conditions there is a reduction in peripheral vascular resistance in the cerebrum during behavioural state 2F in the normal-developing human fetus, suggesting increased cerebral blood flow. The fetal behavioural state should be taken into account in further clinical studies on velocity waveforms in the fetal internal carotid artery during the latter weeks of pregnancy.

Acknowledgement

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4.2 The Doppler flow velocity waveform in the fetal internal carotid artery with respect to fetal behavioural states; A longitudinal study

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Abstract

Doppler flow velocity waveforms in the fetal internal carotid artery were recorded in 21 normal pregnancies during fetal behavioural state 1F (quiet sleep) and 2F (active sleep) according to Nijhuis et al (1982), from the 36th week of gestation onward. The present study confirms the earlier finding of a significant reduction of the pulsatility index (PI) in state 2F as compared to state 1F at 37-38 weeks of gestation (van Eyck et al, 1987) and demonstrates that this difference in PI exists throughout the entire period, in which fetal behavioural states have been described. Furthermore, it is demonstrated that there is a significant reduction in PI of this vessel during the last four weeks of gestation, suggesting a haemodynamic redistribution, favouring blood supply to the brain during the latter weeks of gestation.

Key words: Doppler ultrasound; blood flow velocity waveform; fetal internal carotid artery; fetal behavioural states.

Introduction

Recently, in a cross-sectional study at 37-38 weeks of gestation, it was demonstrated in the normal developing human fetus, that fetal behavioural states affect blood flow velocity waveforms in the descending aorta (van Eyck et al, 1985) and internal carotid artery (van Eyck et al, 1987). Using the classification of Nijhuis et al (1982) the pulsatility index was significantly reduced during behavioural state 2F (active sleep) compared to behavioural state 1F (quiet sleep) suggesting increased cerebral blood flow during state 2F (van Eyck et al, 1987). Well-defined behavioural states appear as from 36 weeks of gestation (Nijhuis et al, 1982).

The question arises as to whether the state dependency of fetal internal carotid blood flow observed in the earlier cross-sectional study is present during the entire latter 4-5 weeks of pregnancy, during which clear behavioural states have been described. It was therefore decided to perform a longitudinal study of the flow velocity waveform in the fetal internal carotid artery from normal pregnancies as from 36 weeks of gestation onward during fetal behavioural state 1F and 2F.

Material and Methods

Subjects

A total of 21 healthy subjects, including 11 primigravidae and 10 multigravidae with singleton pregnancies at 36 weeks of gestation gave informed consent to participate in the study. The gestational age had been calculated from a reliable menstrual history and early ultrasonic measurement of fetal crown-rump length or biparietal diameter. No medication was prescribed. All pregnancies were uneventful, resulting in the delivery of a healthy infant with a birthweight between the 10th and 90th percentile for gestational age according to Kloosterman's Tables (Kloosterman, 1970), corrected for maternal parity and fetal sex.

Measurement procedures

All subjects were studied in the semirecumbent position. A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400) was used for recording maximum flow velocity waveforms in the fetal internal carotid artery (Wladimiroff et al, 1986) during fetal behavioural state 1F (quiet sleep) and 2F (active sleep) as described by Nijhuis et al (1982).
In order to establish these fetal behavioural states, the following parameters were simultaneously recorded:

a. The fetal heart rate (FHR), which was obtained from a Doppler ultrasound cardiotocograph (Hewlett Packard 8040A, carrier frequency 1 MHz);
b. Fetal eye movements which were studied from a transverse view of the fetal face using the Diasonics CV 400 (carrier frequency 3.5 MHz);
c. Fetal body movements, which were obtained from a sagittal view of the fetal trunk, using a 2-dimensional real-time linear array scanner (Toshiba Sal 20A, carrier frequency 3.5 MHz).

The three transducers were placed in such a way, that there was minimal interference between the three ultrasound modes.
Flow velocity recordings were only performed when a clear fetal behavioural state was identified and when this state had been present over a period of at least three minutes. The maximum amount of time allowed between a state determination and the completion of a flow velocity recording was three minutes. All recordings were performed during fetal apnoea. Blood flow velocity waveforms were recorded on videotape. The degree of pulsatility of the recorded waveforms was quantified by calculating the pulsatility index (PI) according to Gosling and King (1975) using a microcomputer (Apple III).

Data collection

Weekly measurement sessions were carried out up to the time of delivery in all 21 subjects. The mean number of sessions was 3.8 (range: 2-5), distributed as follows: 2 weeks, n = 2; 3 weeks, n = 6; 4 weeks, n = 7; 5 weeks, n = 6. In nine participants a total of 14 recordings in either state 1F or 2F had to be rejected due to poor quality or was not obtained at all as a result of excessive body or breathing movements, deep engagement of the fetal head or technical failure of the video-equipment. The mean number of cardiac cycles per recording studied in state 1F was 25.2 (range: 15-46) and in state 2F: 27.1 (range: 12-45).

Statistical procedures

For each patients the weekly measured PI was standardized at a fixed FHR level of 140 bpm by interpolating from a distribution free regression line relating PI to FHR according to Brown and Mood (1951).
Since the data are in longitudinal form, cross-sectional analysis at weekly intervals might be severely misleading (Oldham, 1968). A proper analysis should check for similarity of individual time trends before averaging may be performed.
Conventional regressionlines to relate standardized PI values and gestational age were therefore calculated for each subject provided a minimum of four standardized PI values were available.
The slopes of these regressionlines were compared within behavioural state between primigravidae and multigravidae using the two sample tests of Wilcoxon, and between states 1F and 2F within subjects using the paired signed rank test.
In a next step, the significance of the relationship between standardized PI and gestational age, both in state 1F and 2F, was tested using the sign test applied to the individual slopes of the regression lines. Finally, the mean difference in standardized PI level between states 1F and 2F was tested for significance using the combined signed rank test for the paired observations of PI between 36 and 41 weeks of gestation.

Results

The interpolation from the distribution free regression lines of PI against FHR resulted in 74 standardized PI values (mean: 3.5 per patient; range: 2-5) in state 1F and in 81 standardized PI values (mean: 3.9 per patient; range: 2-5) in state 2F.
Calculation of regression lines relating standardized PI and gestational age was feasible in 12 subjects in state 1F and 12 subjects in state 2F, with 10 common in both groups, resulting in a total of 24 regressionlines (Table I). The slopes of these lines showed no statistically significant difference between primigravidae and multigravidae nor between behavioural states 1F and 2F. Moreover, the mean of the slopes of the twelve regression lines in state 1F and in state 2F did not essentially differ from the calculated slopes of the regression lines for 1F and 2F as presented in Figure 1.
Figure 1 depicts the averaged standardized PI in the fetal internal carotid artery relative to gestational age for the entire study population during behavioural states 1F and 2F.
The standardized PI showed a statistically significant negative correlation with gestational age ($p < 0.01$) both in state 1F and 2F. Throughout the entire study period, standardized PI values during state 2F were significantly lower ($p < 0.01$) than those in state 1F (Fig. 1).

Table I. Slopes of the regression lines relative to parity and behavioural state in 14 subjects.

Subject	Primigravida / multigravida	Slope of regression-line in 1F	Slope of regression-line in 2F
1	M	-0.072	-0.046
3	P	-0.069	-0.034
4	P	-0.185	-0.234
7	M	-0.072	-0.104
9	P	+0.041	-0.023
11	M	-0.023	+0.028
12	P		-0.163
13	P	-0.096	+0.061
14	M	-0.164	-0.135
15	M	-0.095	-0.117
16	P	-0.027	
18	P	-0.137	
19	P	-0.001	-0.099
21	M		-0.082
Mean slope		-0.075	-0.079
Calculated slope derived from Fig. 1		-0.083	-0.073

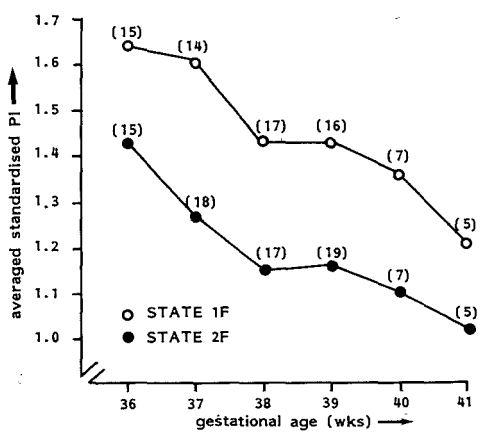

Figure 1. Averaged standardized PI in the fetal internal carotid artery relative to gestational age at weekly intervals during fetal behavioural state 1F and 2F between 36 and 41 weeks (in parentheses: number of subjects).

Discussion

The earlier observation (van Eyck et al, 1987) of a significant reduction in PI during fetal behavioural state 2F compared to 1F at 37-38 weeks of gestation has been confirmed in the present study for the entire period of pregnancy in which well-defined behavioural states have been described.
Whereas in an earlier report (Wladimiroff et al, 1987a) only a downward trend of the PI in the fetal internal carotid artery during the last four weeks of gestation was suggested, the present study demonstrates a statistically significant reduction in PI during this period of pregnancy. Although there is no real discrepancy between these data, it should be realised that only a limited comparison is allowed due to the different study design (cross-sectional versus longitudinal data collection) and the introduction of a PI standardized for fetal heart rate in the present study.
The absence of any statistical difference in slope of the regression lines for the relation between PI and gestational age between state 1F and 2F clearly demonstrates that this reduction in PI during the latter weeks of pregnancy is not essentially different between state 1F and 2F. Apparently parity does not seem to affect the blood flow velocity waveform in the two behavioural states in this gestational age group. The PI in the fetal internal carotid artery may be mainly affected by heart rate, blood pressure and changes in cerebral vascular resistance. In the present study PI was standardized for fetal heart rate. No information is available on blood pressure changes in the human fetus, but mean arterial blood pressure rises during fetal life at different rates in different mammalian species (Dawes, 1968b; MacDonald et al, 1983). There is, however, no reason to believe that a rise in systemic arterial pressure will result in a reduction in PI in the internal carotid artery.
If PI changes are predominantly affected by changes in cerebral vascular resistance, than the documented PI reduction in the present study suggests a haemodynamic redistribution favouring blood supply to the brain during the latter weeks of gestation.
It can be concluded from the present study that there is a significant reduction in PI of the fetal internal carotid artery in state 2F compared to 1F for the entire period of pregnancy in which well-defined behavioural states have been described.
Furthermore there is a significant reduction in PI of this vessel from the 36th week of gestation onward.

Acknowledgement

We are grateful to Dr. F.K. Lotgering for his critical remarks. We thank Diasonics / Sonotron for the use of the Diasonics CV400 and the "Drie Lichten" Foundation for their financial support of this study.

4.3 Cerebral and umbilical arterial blood flow velocity waveforms in normal and growth-retarded pregnancies

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Summary

A combined sector and pulsed Doppler system was used to study the pulsatility index in the fetal internal carotid artery and umbilical artery in 156 normal pregnancies and 42 cases of intrauterine growth retardation (birth weight below the tenth percentile). All pregnancies were in the third trimester. In normal pregnancies, there was a gestational age-related fall in pulsatility index for both the umbilical artery and the umbilical artery /internal carotid artery ratio. No such fall was established for the pulsatility index values in the internal carotid artery. In growth-retarded pregnancies, raised pulsatility index values in the umbilical artery were associated with reduced pulsatility index values in the internal carotid artery, suggesting the presence of a "brain-sparing" effect. When fetal causes of growth retardation were excluded, the sensitivities of the pulsatility index in the internal carotid artery, the umbilical artery, and for the umbilical artery /internal carotid artery ratio were 65, 83, and 88% at the 1 standard deviation (SD) cutoff level; and 48, 60, and 70% at the 2 SD cutoff level. Growth-retarded fetuses with structural or chromosomal defects had normal pulsatility index values in the internal carotid artery. (*Obstet Gynecol 69: 705, 1987*).

Introduction

Since the introduction of combined two-dimensional real-time and pulsed wave Doppler systems, a number of reports have described the blood flow velocity waveform in the fetal descending aorta and umbilical artery in both normal (Gill et al, 1979; Eik-Nes et al, 1980; Tonge et al, 1983) and complicated pregnancies (Griffin et al, 1984; Jouppila et al, 1984; Trudinger et al, 1985b; Schulman et al, 1984). It has been demonstrated that intrauterine growth retardation (IUGR) is associated with reduced end-diastolic flow velocity and elevated pulsatility index in these vessels. Recently, a pulsed Doppler method was introduced for recording the flow velocity waveform in the fetal internal carotid artery (Wladimiroff et al, 1986). In the same study, preliminary data demonstrated a reduced pulsatility index in this flow velocity waveform during IUGR, reflecting decreased vascular resistance in the fetal cerebrum, i.e., a "brain-sparing" effect.

Questions arise as to the sensitivity of the pulsatility index in the internal carotid artery and umbilical artery in identifying IUGR, and whether the sensitivity can be improved by calculating the ratio of the pulsatility indices from both vessels.

The aim of the present study was threefold: 1) to determine the pulsatility index from the normal flow velocity waveforms in the fetal internal carotid artery and umbilical artery during the third trimester of pregnancy; 2) to calculate the ratio between the pulsatility index values from these two vessels; and 3) to establish the sensitivity of the pulsatility index in these vessels and in the umbilical artery /internal carotid artery ratio in the identification of IUGR.

Materials and Methods

A combined mechanical sector and pulsed Doppler system (Diasonics CV 400) with a carrier frequency of 3.5 and 3 MHz was used for blood flow velocity measurements in the internal carotid and umbilical arteries in 156 normal pregnancies and 42 cases of IUGR. Gestational age varied between 26 and 39 weeks. Each patient was certain of the date of onset of her last menstrual period. The maximum flow velocity waveform in the internal carotid artery was obtained at the level of the bifurcation into the middle and anterior cerebral artery. The sample size of the Doppler probe, necessary for sampling frequency shifts originating from the moving erythrocytes within a vessel, was 4 mm. This allowed clear signals from the internal carotid artery without interference from other nearby vessels. The maximum flow velocity waveform in the umbilical artery was documented according to the method of McCallum et al (1978). The degree of pulsatility of the waveform was quantified by calculating the pulsatility index (Gosling et al, 1975). In both flow velocity waveforms, a microcomputer calculated the pulsatility index over at least four consecutive cardiac cycles.

The reproducibility of the flow velocity waveform recordings in the internal carotid artery and umbilical artery was established as follows: The maximum flow velocity waveform was measured ten times within 24 hours in three individual fetuses. The mean pulsatility index of each of these recordings was calculated and the mean standard deviation (SD) determined. All measurements were performed in the semirecumbent position and during periods of apnea, because high-amplitude fetal breathing modulates the blood flow velocity waveforms.

Normal pregnancies were defined by normal biparietal diameters (BPD), head circumference, and upper abdominal circumference measurements according to normograms by Campbell et al (1976), and by a birth weight between the tenth and 90th percentiles for gestational age according to Kloosterman's tables (Kloosterman, 1970), corrected for maternal parity and fetal sex.

Intrauterine growth retardation was defined by: 1) flattening of the growth pattern resulting in a clinical discrepancy of more than two weeks on fundal height on two successive antenatal appointments, and ultrasonic findings of upper abdominal circumference measurements below the tenth percentile in association with normal or reduced head circumference measurement. Head /abdominal ratio values were calculated according to the method of Campbell and Thoms (1977). 2) Postnatal confirmation of IUGR was defined as a birth weight below the tenth percentile for gestational age according to Kloosterman's tables (Kloosterman, 1970), corrected for maternal parity and fetal sex.

In the 42 cases of IUGR, the majority (70%) exhibited an elevated head /abdominal ratio. The mean lag time between blood flow velocity recordings in the group of IUGR and delivery was 23 days (range two to 65 days).

The normal group was divided into seven gestational age periods (Table I). For each study period, we calculated the mean ± 1SD of the pulsatility index in the internal carotid and umbilical arteries, and the pulsatility index ratio between these two vessels. Differences in mean pulsatility index between two age groups were tested by the Mann-Whittney rank sum test. The pulsatility index in the IUGR group was compared with that in the normal study group using the χ^2 test. For each of the vessels, including the umbilical artery /internal carotid artery ratio, the sensitivity of the pulsatility index in identifying IUGR was calculated using 1 SD and 2 SD cutoff levels.

Results

In about 95% of the cases, intra-individual measurements of the pulsatility index in the internal carotid artery fell within ± 0.13 of the expected mean, and in the umbilical artery within ± 0.08, indicating an acceptable degree of reproducibility. Table I presents the mean ± 1SD for the pulsatility index in the internal carotid and umbilical arteries, and the umbilical artery /internal carotid artery ratio for the normal study group. We obtained acceptable flow velocity waveforms for pulsatility index calculations in the internal carotid artery in 116 (74%) and in the umbilical artery in 149 (95%) of the 156 normal subjects. The pulsatility index for the umbilical artery /internal carotid artery ratio could be calculated for 108 subjects (69%). The mean pulsatility index value of 1.67 at 32-33 weeks in the internal carotid artery (Table I) appears to be a cohort effect. Using the Bonferroni adjustment (Glantz, 1981), in which the *P* value for each age group comparison is multiplied by the total number of comparisons (21), we found no significant changes with gestational age in mean pulsatility index in this vessel. Mean pulsatility index in the umbilical artery ranged from 0.79-1.19 ($p < .01$), whereas the mean pulsatility index for the umbilical artery /internal carotid artery ratio varied between 0.57-0.79 ($p < .01$).

Table I. Pulsatility index* for the internal carotid artery, umbilical artery, and umbilical artery / internal carotid artery ratio during the third trimester of pregnancy.

	Internal carotid artery		Umbilical artery		Umbilical artery /internal carotid artery ratio	
Gestational age (wk)	No. of patients	Pulsatility index	No. of patients	Pulsatility index	No. of patients	Pulsatility index
26-27	13	1.55 ± 0.26	15	1.19 ± 0.12	12	0.79 ± 0.20
28-29	8	1.55 ± 0.16	15	1.04 ± 0.14	8	0.69 ± 0.12
30-31	17	1.56 ± 0.26	25	1.04 ± 0.20	16	0.68 ± 0.18
32-33	18	1.67 ± 0.26	25	1.04 ± 0.19	16	0.60 ± 0.14
34-35	22	1.56 ± 0.23	21	0.87 ± 0.14	19	0.59 ± 0.14
36-37	18	1.42 ± 0.35	23	0.79 ± 0.16	17	0.58 ± 0.19
38-39	20	1.40 ± 0.24	25	0.80 ± 0.15	20	0.57 ± 0.15

*Measured as mean ± 1SD.

Of the 42 cases of IUGR, birth weight was situated between the fifth and tenth percentile in ten and below the fifth percentile in 32 cases. Associated findings in this group were: pregnancy-induced hypertension (n = 22) and fetal structural / chromosomal defects (trisomy 18, 69xxx; three cases of renal agenesis; microcephaly). In the remaining 14 cases, no overt maternal of fetal disease was established. Figures 1, 2, and 3 provide the pulsatility index values in the 42 cases of IUGR relative to the normograms constructed from the data in Table I. In 37 cases, a pulsatility index value was obtained from both vessels, allowing calculation of the pulsatility index for the umbilical artery /internal carotid artery ratio. In four cases, a pulsatility index value was collected from the umbilical artery alone, and in one case from the internal carotid artery alone. The six fetuses with structural /chromosomal defects were excluded from the statistical analysis. The pulsatility index demonstrated a significant reduction in the internal carotid artery ($p < .001$) and a significant rise with respect to the umbilical artery /internal carotid artery ratio ($p < .001$). At the 1SD cutoff level, the sensitivity of the pulsatility index in the internal carotid artery was 65%, in the umbilical artery 83%, and for the umbilical artery /internal carotid artery ratio, 88%. At the 2SD cutoff level, the percentages were 48, 60 and 70%, respectively. When only the severely growth-retarded fetuses (birth weight below the fifth percentile) were considered, the percentages were 67, 89, and 96% for the 1SD cutoff; and 50, 71, and 79% for the 2SD cutoff level, respectively.

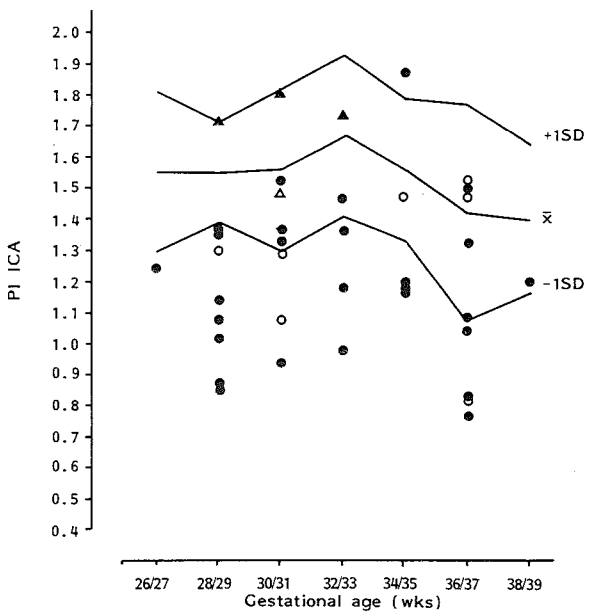

Figure 1. Individual pulsatility index values from 42 growth-retarded pregnancies relative to the normogram for the internal carotid artery. Open circles indicate growth retardation due to placental insufficiency with birth weight in the fifth to tenth percentile; closed circles indicate below the fifth percentile. Open triangles indicate IUGR due to structural / chromosomal defects with birth weight in the fifth to tenth percentile; closed triangles indicate below the fifth percentile.

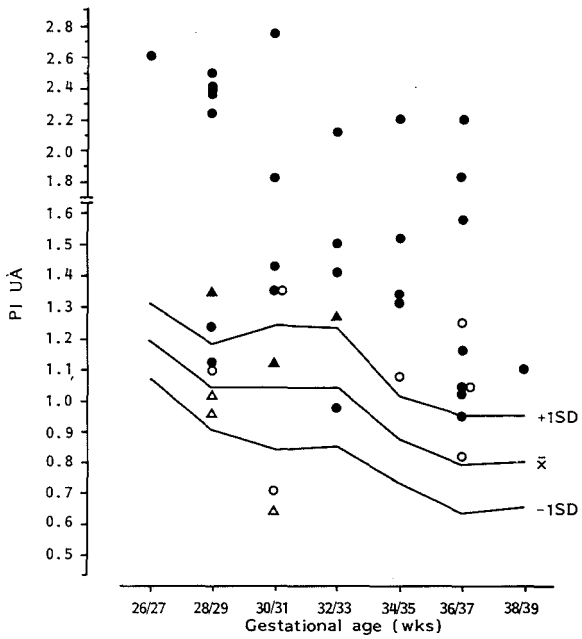

Figure 2. Individual pulsatility index values from 42 growth-retarded pregnancies relative to the normogram for the umbilical artery. Open circles indicate growth retardation due to placental insufficiency with birth weight in the fifth to tenth percentile; closed circles indicate below the fifth percentile. Open triangles indicate IUGR due to structural / chromosomal defects with birth weight in the fifth to tenth percentile; closed triangles indicate below the fifth percentile.

When considering the six fetuses with structural / chromosomal defects, the pulsatility index in the internal carotid artery was always (four out of four) within the normal range. In the umbilical artery, it was above the 1SD level in two out of six cases, and for the umbilical artery / internal carotid artery ratio, it was always below the 1SD level.

Discussion

The normal waveform always displays forward flow because of the low peripheral resistance circulation in the fetus and placenta. While one can almost always visualize the umbilical cord surrounded by amniotic fluid, the fetal internal carotid artery may be difficult to locate because of fetal movements, maternal obesity, or occipito-anterior position of the fetal head.

The gestational age-related decrease of the pulsatility index in the umbilical artery has been reported by others (Trudinger et al, 1985b; Reuwer et al, 1984) and reflects a reduction of flow resistance in the placental villous circulation. The pulsatility index in the internal carotid artery does not display a significant change. The large standard deviation of the pulsatility index, particularly near

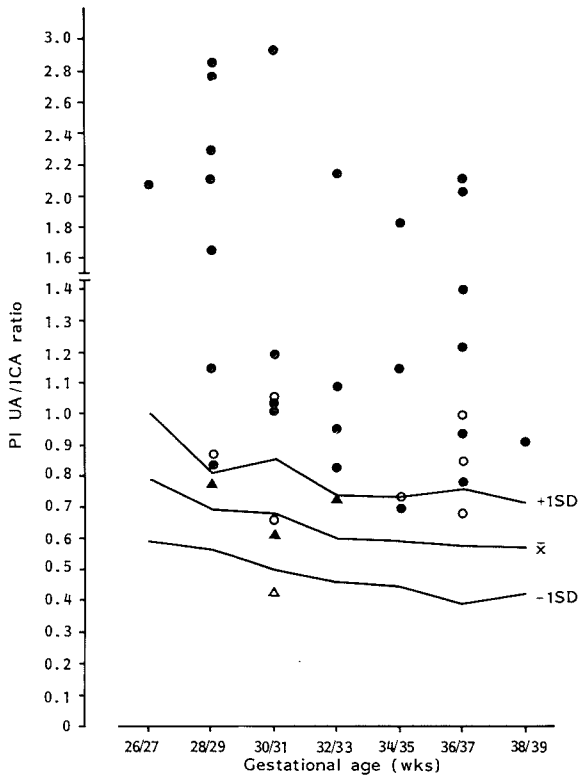

Figure 3. Individual pulsatility index values from 42 growth-retarded pregnancies relative to the normogram for the umbilical artery/internal carotid artery ratio. Open circles indicate growth retardation due to placental insufficiency with birth weight in the fifth to tenth percentile; closed circles indicate below the fifth percentile. Open triangles indicate IUGR due to structural/chromosomal defects with birth weight in the fifth to tenth percentile; closed triangles indicate below the fifth percentile.

term, may be due in part to the effect of the fetal behavioural state on the blood flow velocity waveform (van Eyck et al, 1985). In the fetal descending aorta, a significant difference in pulsatility index between quiet and active sleep states has been observed during normal term pregnancy. Preliminary data suggest a similar pattern in the internal carotid artery. Of interest is that in the normally developing fetus during the third trimester of pregnancy, the level of the pulsatility index in the internal carotid artery is similar to that in the fetal descending aorta (Wladimiroff et al, 1986) (1.7-1.8). The observed reduction in the pulsatility index for the umbilical artery/internal carotid artery ratio with gestational age is determined mainly by the pulsatility index changes in the umbilical artery.

In growth-retarded pregnancies, there is a marked elevation in pulsatility index in the umbilical artery and a marked decrease in pulsatility index in the fetal internal carotid artery. These changes are predominantly due to changes in end-diastolic flow velocity, and confirm earlier data (Wladimiroff et al, 1986)

suggesting a "brain-sparing" effect in the presence of IUGR. The sensitivity of the pulsatility index calculations from the flow velocity waveforms in the umbilical artery appears to be superior to that in the internal carotid artery, and the umbilical artery /internal carotid artery ratio is the most sensitive. Others (Reuwer et al, 1984) have pointed out that the pulsatility index in the umbilical artery may even be raised several weeks or months before IUGR is clinically suspected. Although ultrasound measurements of the fetal upper abdomen have greatly improved the early detection of IUGR, we feel that based on the above flow data, it may be worth testing the hypothesis that pulsatility index changes in these vessels occur at a very early stage of placental insufficiency, i.e., well before IUGR is manifest. Therefore, one should carry out early simultaneous pulsatility index determinations in the umbilical and internal carotid arteries in high-risk pregnancies.

Of interest are the six growth-retarded fetuses with structural chromosomal defects. Although small in number, all four pulsatility index values in the internal carotid artery were situated within the normal range, suggesting the absence of a brain-sparing effect. The pulsatility index in the umbilical artery was raised in two of six cases, which supports a larger study by Trudinger et al (Trudinger et al, 1985c) demonstrating that a raised pulsatility index in the umbilical artery may also occur in growth-retarded fetuses with structural defects. More data are needed to establish the significance of pulsatility index determinations in the fetal internal carotid artery for differentiating between placental and fetal causes of growth retardation.

We conclude that in both the umbilical and fetal internal carotid arteries, it is possible to make reproducible pulsatility index determinations. These determinations in the latter vessel have provided direct evidence of the brain-sparing effect in the growth-retarded human fetus. In contrast to the umbilical artery and umbilical artery /internal carotid artery ratio, the pulsatility index in the internal carotid artery exhibits a poor sensitivity in identifying IUGR.

4.4 The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relationship to fetal behavioural states in the growth retarded fetus at 37-38 weeks of gestation

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Summary

In eight patients with intrauterine growth retardation (IUGR), the relationship between the blood flow velocity waveform in the fetal internal carotid and umbilical artery and fetal behavioural states at 37-38 weeks of gestation was studied. In both vessels there is a virtual overlap of Pulsatility Index (PI) values originating from state 1F and 2F according to the classification by Nijhuis et al (1982), reflecting behavioural state independency. In the internal carotid artery this state independency is associated with moderately reduced PI values.

Introduction

Nijhuis et al (1982) were the first to provide clear evidence for the existence of behavioural states in the human fetus during the last weeks of pregnancy.
It was demonstrated in previous studies that in normal pregnancies at 37-38 weeks of gestation, blood flow velocity waveforms in the lower thoracic part of the fetal descending aorta (van Eyck et al, 1985) and internal carotid artery (van Eyck et al, 1987) are affected by these behavioural states. In the umbilical artery no such state dependency could be established, suggesting a fetal origin of the observed aortic and carotid blood flow changes (van Eyck et al, 1987).
In intrauterine growth retardation (IUGR), flow velocity waveform changes have been documented in the fetal descending aorta, umbilical artery and internal carotid artery, suggesting the presence of increased peripheral vascular resistance at the fetal trunk and placental level (Griffin et al, 1984; Reuwer et al, 1984; Trudinger et al, 1985a; Tonge et al, 1986b) associated with reduced vascular resistance in the fetal cerebrum (Wladimiroff et al, 1986). Of interest is that as opposed to normal pregnancy no state dependency could be documented for the fetal descending aorta in IUGR (van Eyck et al, 1986). The objective of the present study was to establish whether state independency was also present in the fetal internal carotid artery and umbilical artery during IUGR.

Patients and Methods

A total of eight patients with IUGR in singleton pregnancies at 37-38 weeks

of gestation gave consent to participate in the study. The gestational age had been calculated from a reliable menstrual history and early ultrasonic measurement of fetal crown-rump length or biparietal diameter. IUGR was defined as a progressive asymmetric slow-down in increase of fetal head and upper abdominal circumference resulting in values below the 5th percentile of the nomograms by Campbell and Wilkin (1977). Maternal diastolic blood pressure was raised ($>$ 90 mm Hg) in five out of eight patients.
No medication was prescribed. There was no serological evidence of fetal infection. There were no signs of fetal distress during the behavioural studies. Gestational age at delivery ranged between 39 and 41 weeks. Fetal distress as expressed by late FHR-decelerations presented during labour in six out of eight patients resulting in Caesarean Section in four and forceps extraction or fundal expression in the remaining two patients. Fetal birth weight was below the 5th percentile for gestational age according to Kloosterman's Tables (Kloosterman, 1970), corrections being made for maternal parity and fetal sex. There were no congenital abnormalities. The Apgarscore at one minute was $\geqslant$ 5, at five minutes $\geqslant$ 8.
All patients were studied in the semirecumbent position. A combined mechanical sector scanner and pulsed Doppler system (Diasonics CV 400) was used for recording maximum flow velocity waveforms in the fetal internal carotid and umbilical artery during fetal behavioural states 1F (quiet sleep) and 2F (active sleep) as described by Nijhuis et al (1982).
In order to establish these fetal behavioural states, the following parameters were simultaneously recorded: a) The fetal heart rate (FHR), which was obtained from a Doppler ultrasound Cardiotocograph (Hewlett Packard 8040A, carrier frequency 1 MHz); b) Fetal eye movements which were studied from a transverse view of the fetal face using the Diasonics CV 400 (carrier frequency 3.5 Mhz); c) Fetal body movements which were obtained from a sagittal view of the fetal trunk, using a 2-dimensional real-time linear array scanner (Toshiba Sal 20A, carrier frequency 3.5 MHz).
The three transducers were placed in such a way, that there was minimal interference between the three ultrasound modes. We found a stable combination of the three state variables with short transitions within three minutes. Our patients therefore displayed true behavioural states and not only coincidence of the variables. Flow velocity recordings were only performed when a true fetal behavioural state was identified and when this state had been present over a period of at least three minutes. All recordings were started two hours following the evening meal and were performed during fetal apnoea. The maximum amount of time allowed between a state determination and the completion of a flow velocity recording was three minutes. Blood flow velocity waveforms were recorded on videotape over a 15-second period which included an average of 20 consecutive cardiac cycles. In each subject a minimum of three flow velocity waveform recordings in each vessel in each behavioural state (1F and 2F) was obtained. From hard copies of each flow velocity recording on average 15 cardiac cycles of optimal quality were selected. The degree of pulsatility of the waveform was quantified by calculating the pulsatility index (PI) according to Gosling and King (1975) using a microcomputer (Apple III). Cardiac cycle length dependency of the PI was ruled out by dividing the PI values in each subject

and for each fetal behavioural state into groups, each of which representing a FHR range of 5 bpm. Changes in PI values with respect to the fetal behavioural state were tested using the paired Student's t test and the 95% confidence limit. The relation between PI and FHR was tested by analysing the slopes of the individual regression lines by means of the Student's t test.

Results

The mean number of cardiac cycles studied in the fetal internal carotid artery for all eight subjects was 50 (min. 31; max. 72) in state 1F and 48 (min. 29; max. 63) in state 2F, a total of 782 cycles. FHR in state 1F ranged between 98 and 158 bpm and in state 2F between 115 and 167 bpm. When calculating the mean PI independent of FHR and behavioural state, all eight values were situated below -1SD and in two patients below -2SD of the normogram according to Wladimiroff et al (1987a).
The mean number of cardiac cycles studied in the umbilical artery was 47 (min. 15; max. 66) in state 1F and 41 (min. 18; max. 62) in state 2F, a total of 699 cycles. FHR in state 1F ranged between 99 and 171 bpm and in state 2F between 107 and 162 bpm. The mean PI irrespective of FHR and behavioural state was situated above +1SD in all eight patients and above +2SD in five patients according to the normogram by Wladimiroff et al (1987a).
Paired analysis of the PI data in state 1F and 2F was feasible for the fetal internal carotid artery in the FHR range between 126 and 145 bpm (561 cardiac cycles) and for the umbilical artery also in the FHR range between 126 and 145 bpm (529 cardiac cycles). There was no statistically significant difference in mean PI between state 1F and 2F for all FHR ranges studied in the fetal internal carotid artery (Table I) and umbilical artery (Table II). Moreover the

Table I. Mean paired PI difference ($\Delta PI \pm 1SD$) and 95% confidence interval between fetal behavioural states 1F and 2F in the FHR range between 126 and 145 bpm in the fetal internal carotid artery in IUGR.

FHR range (bpm)	Number of paired observations	Mean PI		ΔPI	SD	Significance	95% confidence interval
		State 1F	State 2F				
126-130	7	1.09	1.14	-0.05	0.28	$p > 0.20$ (NS)	-0.31,0.21
131-135	7	1.05	1.14	-0.09	0.22	$p > 0.20$ (NS)	-0.29,0.11
136-140	8	1.01	1.07	-0.06	0.18	$p > 0.20$ (NS)	-0.21,0.09
141-145	7	0.97	1.10	-0.13	0.21	$p > 0.10$ (NS)	-0.33, 0.07

95% confidence interval of the paired differences in mean PI between state 1F and 2F displayed for each FHR range a narrow distribution around zero, reflecting a virtual overlap of PI values originating from state 1F and 2F. Figures 1 and 2 demonstrate for the fetal internal carotid artery and umbilical artery the regression lines for the relationship between PI and FHR in state 1F and 2F for all eight subjects. The length of the lines indicates the range of the observed data. A significant inverse relationship between PI and FHR was established

for both behavioural state 1F ($p < 0.001$) and 2F ($p < 0.01$) in the umbilical artery and for behavioural state 1F ($p < 0.001$) in the fetal internal carotid artery.

Table II. Mean paired PI difference ($\Delta PI \pm 1SD$) and 95% confidence interval between fetal behavioural states 1F and 2F in the FHR range between 126 and 145 bpm in the umbilical artery in IUGR.

FHR range (bpm)	Number of paired observations	Mean PI State 1F	Mean PI State 2F	ΔPI	SD	Significance	95% confidence interval
126-130	5	1.13	1.17	-0.04	0.15	$p > 0.20$ (NS)	-0.23,0.15
131-135	6	1.26	1.27	-0.01	0.10	$p > 0.20$ (NS)	-0.11,0.09
136-140	7	1.24	1.23	0.01	0.13	$p > 0.20$ (NS)	-0.11,0.13
141-145	6	1.20	1.19	-0.01	0.13	$p > 0.20$ (NS)	-0.15, 0.13

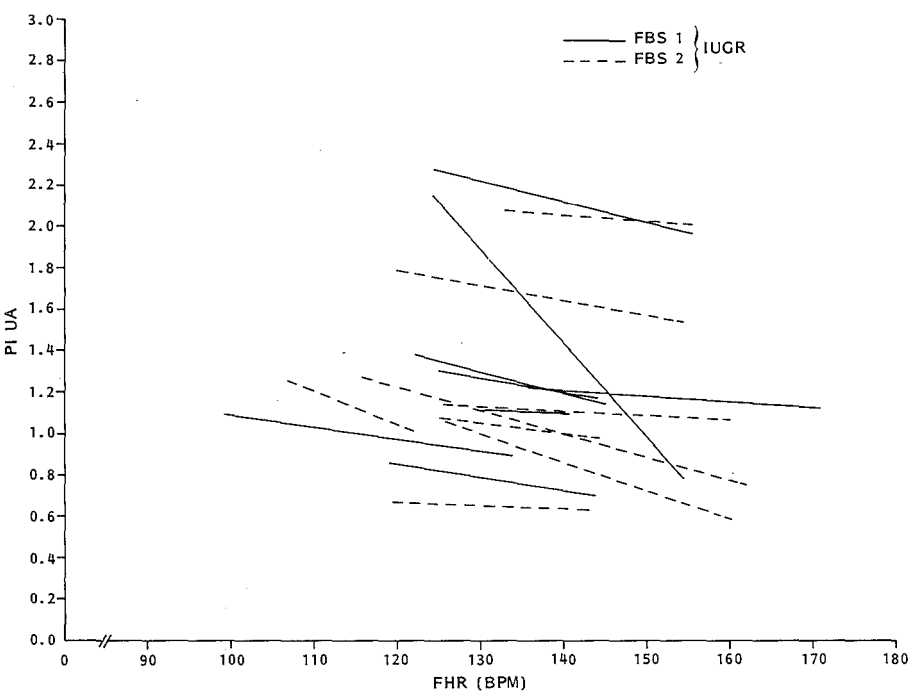

Figure 1. Regression lines for the correlation between PI and FHR in fetal behavioural state 1F (continuous lines) and 2F (dotted lines) in the fetal internal carotid artery.

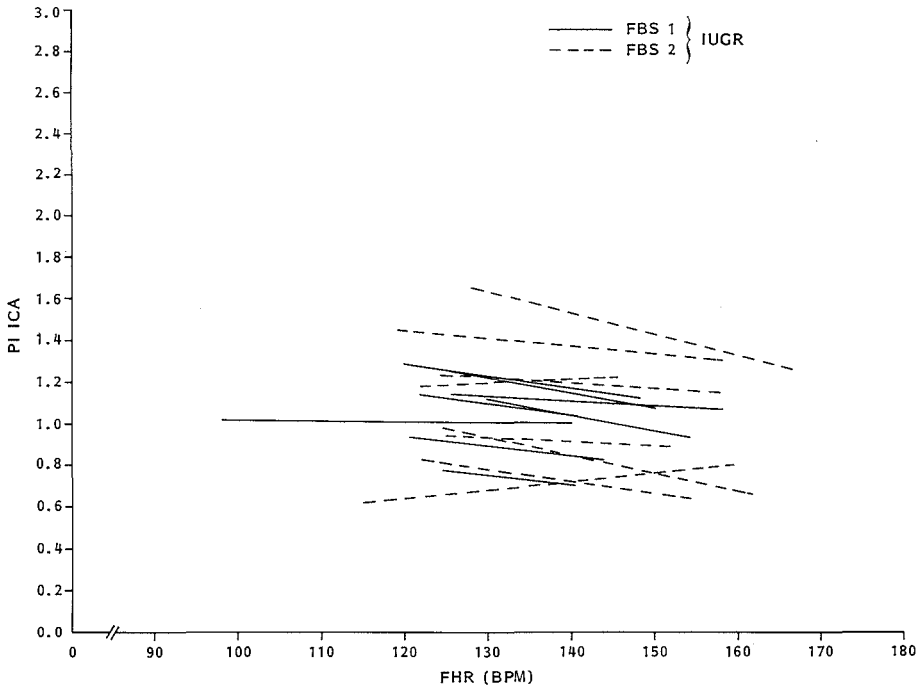

Figure 2. Regression lines for the correlation between PI and FHR in fetal behavioural state 1F (continuous lines) and 2F (dotted lines) in the umbilical artery.

Discussion

All eight fetuses in the present study displayed growth retardation expressed by asymmetric slow-down in increase of fetal head and upper-abdominal circumference and a birthweight below the 5th percentile for gestational age according to Kloosterman's Tables (Kloosterman, 1970), corrections being made for maternal parity and fetal sex.

Although there were no signs of fetal distress at the time of the behavioural studies, six out of eight fetuses displayed abnormal heart rate patterns during labour resulting in assisted vaginal delivery or Caesarean Section. True fetal behavioural states were established in all eight pregnancies, similar to an earlier study in which well-defined behavioural states were related to blood flow in the fetal descending aorta during IUGR (van Eyck et al, 1986).

Recently, flow measurements in the fetal internal carotid artery of normal pregnancies demonstrated reduced PI values during state 2F, reflecting a decrease in cerebral vascular resistance during this behavioural state (van Eyck et al, 1987). According to the present study, this state dependency is absent during IUGR. Similar observations were done in the fetal descending aorta during IUGR

(van Eyck et al, 1986), whereby state independency was nearly always associated with markedly raised PI values. It was suggested that state dependency in this vessel is overruled by stimulation of peripheral chemoreceptors and subsequent release of vasoconstrictive agents, such as vasopressin and catecholamines.
In contrast to the marked PI increase in the fetal descending aorta, state independency in the fetal internal carotid artery was associated with only moderate reduction in PI, suggesting the onset of circulatory redistribution with the aim of favouring cerebral blood flow (brain sparing effect). The degree of PI reduction at this stage seems, however, to be sufficient to overrule behavioural state dependency. Whereas in the fetal internal carotid artery and descending aorta, blood flow velocity patterns changed from state dependency in normal pregnancy into state independency in IUGR, blood flow velocity patterns in the umbilical artery displayed behavioural state independency both in normal pregnancy and IUGR. This strongly suggests a fetal origin of the behavioural state related changes in aortic and carotid blood flow. The inverse relationship between pulsatility index and fetal heart rate for both state 1F and 2F in the umbilical artery and for state 1F in the fetal internal carotid artery is mainly determined by the cycle length dependency of the formula from which the pulsatility index is calculated. This cycle length dependency is mainly due to changes in end diastolic velocity in relation to FHR (van Eyck et al, 1985). The differences between umbilical and internal carotid artery with respect to the statistical significance of the inverse correlation between pulsatility index and fetal heart rate can be explained by the lower absolute pulsatility index values in the latter vessel resulting in a reduced slope of the regression line. This is in agreement with earlier studies in the fetal internal carotid artery, descending aorta and umbilical artery (van Eyck et al, 1985; 1986; 1987), in which higher PI values are associated with steeper slopes, the steepest slope of the regression line being established in the fetal descending aorta during IUGR.
It can be concluded, that in the presence of IUGR, blood flow in the fetal internal carotid and umbilical artery is behavioural state independent. In the internal carotid artery this state independency is associated with only moderate reduction in pulsatility index.

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Chapter 5

CONCLUSIONS

In this thesis the relationship was studied between blood flow velocity waveforms in various fetal vessels and fetal behavioural states, in particular state 1F and 2F according to the classification of Nijhuis et al (1982). In the normal growing human fetus at term, blood flow velocity waveforms obtained from the lower thoracic part of the fetal descending aorta show fetal behavioural state dependency. In state 2F pulsatility index values are statistically significant reduced as compared with state 1F. This reduction in pulsatility index is mainly determined by a rise in end-diastolic velocity. The reduced pulsatility index and elevated EDV reflect a reduced peripheral vascular resistance, suggesting increased perfusion of skeletal musculature. The reduced pulsatility index in the fetal internal carotid artery in fetal behavioural state 2F in the normal growing human fetus at term suggests increased cerebral perfusion. Due to the increased muscular and electrocortical activity in behavioural state 2F, there is a raised energy demand. During the last four weeks of pregnancy there is a fall in pulsatility index in the fetal internal carotid artery with maintainance of behavioural state dependency. Fetal behavioural state dependency should be taken into account when blood flow velocity waveforms in the lower thoracic part of the fetal descending aorta and fetal internal carotid artery are studied in the normal growing human fetus at term. At 27-28 weeks of gestation, the pulsatility index in the lower thoracic part of the fetal descending aorta displays a statistically significant reduction during periods with high fetal heart rate variability as compared with periods with low fetal heart rate variability, irrespective of fetal eye or body movements.

It is suggested that baroreceptor sensitivity is related to pulsatility index fluctuations in different fetal behavioural states in general and fetal heart rate variability in particular.

The fetal origin of the behavioural state dependent pulsatility index fluctuations in the normal growing fetus at term is suggested by the absence of behavioural state dependent pulsatility index fluctuations in the umbilical artery. This state independency in the umbilical artery is of practical importance, since in contrast to the above mentioned fetal vessels, blood flow velocity waveform studies in the umbilical artery during the latter weeks of gestation, may be carried-out without taking the fetal behavioural state into account.

In intrauterine growth retardation (IUGR), the pulsatility index in the lower thoracic part of the fetal descending aorta and in the fetal internal carotid artery show no fetal behavioural state dependency. This may be considered a vascular adaptation, which is instrumental in the redistribution of the fetal circulation during IUGR. The rise in pulsatility index in the lower thoracic part of the fetal descending aorta and the reduction in pulsatility index in the fetal internal carotid artery, which reflect this redistribution, seem to overrule behavioural state dependent pulsatility index fluctuations.

In all studies there is a significant inverse relationship between pulsatility index and fetal heart rate. With increasing fetal heart rate pulsatility index drops. Fetal heart rate should therefore, be taken into account when evaluating blood flow velocity waveforms.

SUMMARY

Chapter 1

The combined use of real-time and pulsed Doppler ultrasound systems has opened the possibility to study blood flow velocity waveforms in various fetal vessels. For a correct interpretation of recorded data it is of importance to establish the effect of internal variables. Nijhuis et al (1982) were able to demonstrate behavioural states in the human fetus at term. Objective of the present study was to investigate the relationship between blood flow velocity waveforms in the lower thoracic part of the fetal descending aorta, fetal internal carotid and umbilical artery and fetal behavioural states, in particular state 1F and 2F according to Nijhuis et al, in the normal growing and growth retarded fetus at term.
Another objective was to investigate the relationship between blood flow velocity waveforms in the lower thoracic part of the fetal descending aorta and separate state variables in the normal growing human fetus at 27-28 weeks of gestation.

Chapter 2

A literature survey is presented on human and animal experimental data concerning maturational aspects of fetal behavioural, particular in relation to the cardiovascular system. Furthermore, data are presented on the relationship between fetal behavioural states and intrauterine growth retardation (IUGR). Virtually no information is available on possible changes in fetal blood flow relative to fetal behavioural states.

Chapter 3

In the human fetus at term, the blood flow velocity waveform in the lower thoracic part of the fetal descending aorta was studied in relation to fetal behavioural states. In the normal growing fetus pulsatility index displays a statistically significant reduction in state 2F as compared with state 1F. This reduction in Pulsatility Index is mainly determined by a rise in end-diastolic velocity. It is suggested that these changes reflect increased perfusion of skeletal musculature. Due to the increased muscular activity in behavioural state 2F there is a raised energy demand. In the growth-retarded human fetus at term the blood flow velocity waveform in the lower thoracic part of the fetal descending aorta shows a raised pulsatility index and no fetal behavioural state dependency. It is suggested that these observations are instrumental in the redistribution of fetal circulation during IUGR. In the normal growing human fetus at 27-28 weeks of gestation the relationship between the blood flow velocity waveform in the lower thoracic part of the fetal descending aorta and separate state variables was studied. The pulsatility index displays a statistically significant reduction

in periods with high heart rate variability compared with periods with low heart rate variability, irrespective of fetal eye and body movements. There is an inverse relationship between fetal heart rate and pulsatility index, which is more pronounced in IUGR than in normal growth.

Chapter 4

Recently Wladimiroff et al (1986) introduced a pulsed Doppler method for recording blood flow velocity waveforms in the human fetal internal carotid artery. A cross-sectional and longitudinal study was performed on the relationship between blood flow velocity waveforms and fetal behavioural state 1F and 2F. In the normal growing fetus at term, pulsatility index values in state 2F show a statistically significant reduction as compared with state 1F, suggesting an increased perfusion of the fetal cerebrum. In behavioural state 2F there is an increased electrocortical activity resulting in a raised energy demand. During the last four weeks of pregnancy a significant fall in pulsatility index is observed. In the growth retarded human fetus, pulsatility index in the internal carotid artery is reduced, suggesting a compensatory reduction in peripheral vascular resistance in the fetal cerebrum, i.e. a brain-sparing effect in the presence of fetal hypoxia. However, in contrast to the umbilical artery and umbilical artery /internal carotid artery ratio, the pulsatility index in the fetal internal carotid artery exhibits a poor sensitivity in identifying IUGR. The presence of reduced pulsatility index in the fetal internal carotid artery seems to overrule fetal behavioural state dependency in this vessel in IUGR. In the umbilical artery, the pulsatility index shows fetal behavioural state independency both in normal growth and in IUGR. This suggests a fetal origin of the observed fetal behavioural state dependent pulsatility index fluctuations in the fetal descending aorta and fetal internal carotid artery. Both in the fetal internal carotid artery and umbilical artery an inverse relationship between fetal heart rate and pulsatility index was established.

SAMENVATTING

Hoofdstuk 1

Het gecombineerde gebruik van real-time en pulsed Doppler echo apparatuur heeft de mogelijkheid geboden om bloedstroomsnelheidsprofielen in verschillende foetale vaten te bestuderen. Voor een juiste interpretatie van de verkregen gegevens is het van belang om het effect van interne variabelen vast te stellen. Nijhuis e.a. (1982) waren in staat om gedragstoestanden bij de à terme humane foetus aan te tonen. Doel van deze studie was de relatie vast te stellen tussen het bloedstroomsnelheidsprofiel in het laag thoracale deel van de foetale aorta descendens, foetale arteria carotis interna en arteria umbilicalis en foetale gedragstoestanden, met name gedragstoestanden 1F en 2F volgens de classificatie van Nijhuis e.a. in de normaal groeiende en groeivertraagde à terme humane foetus. Een ander doel was de relatie vast te stellen tussen het bloedstroomsnelheidsprofiel in het laag thoracale deel van de foetale aorta descendens en afzonderlijke gedragstoestandvariabelen in de normaal groeiende humane foetus bij een zwangerschapsduur van 27-28 weken.

Hoofdstuk 2

Een literatuuroverzicht wordt gegeven van humane en dierexperimentele gegevens, betreffende ontwikkeling van foetaal gedrag, met name in relatie tot het cardiovasculaire systeem. Tevens worden gegevens gepresenteerd over de relatie tussen foetale gedragstoestanden en intrauteriene groeiachterstand. Nagenoeg geen informatie is aanwezig over mogelijke veranderingen in foetale doorbloeding en foetale gedragstoestanden.

Hoofdstuk 3

In de à terme humane foetus werd het bloedstroomsnelheidsprofiel in het laag thoracale deel van de foetale aorta descendens bestudeerd in relatie tot foetale gedragstoestanden. Bij de normaal groeiende foetus was de pulsatility index statistisch significant lager in gedragstoestand 2F vergeleken bij gedragstoestand 1F. Deze pulsatility index daling werd voornamelijk bepaald door een toename in einddiastolische stroomsnelheid. Het wordt gesuggereerd dat deze verandering een verhoogde perfusie van de foetale musculatuur weerspiegelt. Ten gevolge van de verhoogde spierarbeid in gedragstoestand 2F is er een toegenomen energiebehoefte. Bij de groeivertraagde à terme humane foetus toont het bloedstroomsnelheidsprofiel in het laag thoracale deel van de foetale aorta descendens een verhoogde pulsatility index, die gedragstoestand onafhankelijk is. Het wordt gesuggereerd dat deze bevindingen instrumenteel zijn bij de redistributie van de foetale circulatie tijdens intrauteriene groeiachterstand. Bij de normaal groeiende foetus werd bij een zwangerschapsduur van 27-28 weken

de relatie tussen het bloedstroomsnelheidsprofiel in het laag thoracale deel van de foetale aorta descendens en afzonderlijke gedragstoestandvariabelen bestudeerd. De pulsatility index was statistisch significant verlaagd tijdens perioden met verhoogde hartslagvariabiliteit vergeleken bij perioden met verlaagde hartslagvariabiliteit, ongeacht foetale oog- en lichaamsbewegingen. Foetale hartslagfrequentie is omgekeerd evenredig met pulsatility index, hetgeen meer uitgesproken is tijdens intrauterine groeivertraging dan bij normale groei.

Hoofdstuk 4

Onlangs introduceerden Wladimiroff e.a. (1986) een pulsed Doppler methode om het bloedstroomsnelheidsprofiel af te leiden in de humane foetale arteria carotis interna. De relatie tussen het bloedstroomsnelheidsprofiel en gedragstoestand 1F en 2F werd transversaal en longitudinaal bestudeerd. Bij de normaal groeiende à terme foetus was de pulsatility index in gedragstoestand 2F statistisch significant verlaagd vergeleken bij gedragstoestand 1F, hetgeen een toegenomen perfusie van het foetale cerebrum suggereert. In gedragstoestand 2F is er een verhoogde elektrische hersenaktiviteit, resulterende in een toegenomen energiebehoefte. Tijdens de laatste vier weken van de zwangerschap werd een significante daling van de pulsatility index waargenomen. Bij de groeivertraagde foetus is de pulsatility index in de arteria carotis interna verlaagd, hetgeen een compensatoire verlaging van de perifere vaatweerstand in het foetale cerebrum suggereert, met andere woorden een hersensparend effect in de aanwezigheid van foetale hypoxie. Echter, in tegenstelling tot de arteria umbilicalis en arteria umbilicalis /arteria carotis interna ratio, toont de pulsatility index in de arteria carotis interna een slechte sensitiviteit bij de identificatie van intrauteriene groeivertraging. De verlaagde pulsatility index in de foetale arteria carotis interna lijkt foetale gedragstoestandafhankelijkheid te overstemmen. In de arteria umbilicalis vertoont de pulsatility index gedragstoestandonafhankelijkheid bij zowel normale groei als bij intrauteriene groeivertraging. Dit suggereert een foetale origine van de waargenomen gedragstoestand afhankelijke pulsatility index fluctuaties in de foetale aorta descendens en foetale arteria carotis interna. Zowel in de foetale arteria carotis interna en arteria umbilicalis is de foetale hartslagfrequentie omgekeerd evenredig met de pulsatility index.

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