CARDIAC AND EXTRA-CARDIAC FLOW VELOCITY WAVEFORMS
IN THE GROWTH-RETARDED HUMAN FETUS

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CARDIALE EN EXTRA-CARDIALE BLOEDSTROOMSNELHEIDSPROFIELEN IN DE GROEIVERTRAAGDE HUMANE FOETUS

DOOR

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Chapter 1

Introduction and definition of objectives.

Intrauterine growth retardation (IUGR) affects 3% to 10% of all pregnancies. The incidence varies depending on the definition of IUGR. The most frequently used definition is a birth weight less than the 10th percentile for gestational age. Other definitions include birth weight below the 5th, 3rd, 2.5th or 2.3th percentile, more than 2 standard deviations below the mean and ponderal index below the 10th percentile (Seeds, 1984). However, in practice these definitions do not include all growth-retarded fetuses and include constitutionally small fetuses. IUGR is best defined as the failure of a fetus to achieve its growth potential. Growth-retarded fetuses represent a heterogeneous group with respect to the nature, onset, and duration of the insult restricting growth (Chiswick, 1985).

Low birth weight is closely associated with perinatal mortality and long and short-term infant morbidity (Low et al., 1978). Since the frequency of disease such as erythroblastosis fetalis has declined considerably and the survival of premature infants has improved greatly, IUGR is becoming an increasingly significant factor in perinatal mortality and currently ranks second to prematurity as a cause of perinatal loss. Although congenital anomalies are associated with approximately one third of still-births among growth-retarded fetuses, perinatal asphyxia remains the prime cause of perinatal mortality and morbidity in the growth-retarded infant (Wolfe and Gross, 1989).

Under conditions of uteroplacental insufficiency there will be decreased nutrient supply from the mother resulting in a slow-down of the deposition of fat and glycogen stores in the developing fetus. Impairment of both gas exchange and clearance of fetal metabolites means that the growth-retarded fetus may suffer variable degrees of metabolic acidosis and exhibit abnormally low pO_2 levels prior to labour. The decreased reserve poses an additional risk to the fetus during the process of labour. The transient reduction of maternal blood flow during uterine contractions may decrease fetal pO_2 below a critical level and result in abnormal heart rate patterns and acidosis (Wolfe and Gross, 1989). The growth-retarded fetus is also at risk of meconium aspiration which commonly occurs during delivery. An incidence of symptomatic meconium aspiration of 1% to 3% with a neonatal mortality rate approaching 30% has been reported (Bacsik, 1977). The association of oligohydramnios with fetal growth retardation has recently been recognized with the incidence of IUGR in true oligohydramnios approaching 40% (Chamberlain et al., 1984). Oligohydramnios poses an additional risk for fetal and neonatal mortality (Bastide et al., 1986).

Antenatal diagnosis of IUGR is difficult and inaccurate (Hall et al., 1980; Villar and Belizán, 1986). Traditionally, fetal growth is being assessed by measurement of fundal height. The method has been shown to be of limited value for monitoring fetal growth and for diagnosing IUGR. However, when carefully used this low-cost method is a useful tool (Belizán et al., 1990). Ultrasonography has improved the accuracy in the diagnosis of IUGR, with emphasis on the measurement of fetal upper abdominal circumference or area (Campbell and Thoms, 1977; Stoutenbeek, 1982). However, also this method does not reach 100% accuracy.

Recently, more information has become available on changes in fetal behaviour and the cardiovascular system with progressive deterioration of fetal condition in IUGR. In an effort to define a rank order in which cardiovascular and behavioural changes occur with progressive fetal hypoxemia, it became clear that the occurrence of late heart rate decelerations is a good marker of fetal compromise (Bekedam, 1989). In small-for-gestational age fetuses, heart rate accelerations, baseline variation and decelerations have been related to blood gases obtained at cordocentesis (Visser et al., 1990). All three variables had almost the same positive and negative predictive value for fetal hypoxemia and acidemia. A repetitive decelerative pattern best identified the hypoxemic fetus.

Doppler examination of the umbilical arteries allows non-invasive exploration of fetoplacental hemodynamics (Trudinger et al., 1985; Reuwer et al., 1987; Sijmons et al., 1989). The pulsatility of umbilical artery flow reflects downstream placental impedance to flow. Abnormal umbilical artery waveforms as expressed by raised pulsatility are thought to reflect increased vascular placental resistance. The efficacy of Doppler examinations of umbilical arteries as a screening procedure for predicting small-for-gestational age and underweight-for-length (low ponderal index) infants appears to be disappointing with in one study a sensitivity varying from 16.9% for birth weights below the 10th percentile at 28 weeks of gestation to 41.7% for birth weights below 2.3th percentile at 34 weeks of gestation (Sijmons et al., 1989).

Doppler flow velocity waveforms can be recorded at various levels of the fetal cardiovascular system such as the fetal descending aorta (Eik-Nes et al., 1980; Griffin et al., 1984; Jouppila et al., 1984; Maršál et al., 1984; Pijpers, 1985; Tonge, 1987; van Vugt et al., 1987), the internal carotid artery (Wladimiroff et al., 1986), the atrioventricular valves and outflow tract (Kenny et al., 1986; Reed et al., 1986;1987; Allan et al., 1987; De Smedt et al., 1987), the renal arteries (Vyas et al., 1989) and external iliac arteries (Stewart et al., 1990).

Hemodynamic redistribution with preferential blood flow to the brain, my-ocardium and adrenal glands has been described in the chronically hypoxic fetal lamb (Peeters et al., 1979). Doppler flow studies in the internal carotid artery (Wladimiroff et al., 1986) and middle cerebral artery (Woo et al., 1987; Vyas et al., 1990) suggest preferential blood flow to the brain in the presence of growth retardation.

The central theme in this thesis is the documentation of Doppler flow velocity waveforms in a number of cardiac and extra-cardiac arterial vessels with emphasis on changes in the flow velocity waveforms relative to intrauterine growth retardation and fetal and neonatal condition.

The following questions were addressed:

1) What is the reproducibility of flow velocity waveform recording in the fetal cardiac outflow tract (ascending aorta, pulmonary artery, ductus arteriosus); (Chapter 3);

2) Do flow velocity waveforms from the fetal cardiac outflow tract depict changes in the presence of intrauterine growth retardation. If so, how do these changes relate to changes in flow velocity waveforms from the umbilical artery; (Chapter 4);

3) How do fetal cardiac and extra-cardiac flow velocity waveforms relate to (i) fetal heart rate patterns in predicting fetal distress and (ii) neonatal outcome in intrauterine growth retardation; (Chapter 5).

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Chapter 2

Methodological and animal experimental aspects of fetal hemodynamics relative to growth retardation.

Recent developments in Doppler equipment have made it possible to investigate human fetal cardiovascular dynamics without the risk of damaging the fetus. After the first enthusiastic reports in the early eighties, the limitations of this technique have become more clear and the possible applications are being evaluated.

This chapter consists of two parts. The first part will deal with the methodology of Doppler measurements, in particular the analysis of flow velocity waveforms and volume flow calculations. In the second part data on cardiovascular responses to hypoxic stress derived from acute and chronic animal models will be discussed.

2.1 Methodology of Doppler measurements: analyzing the velocity waveform or calculating volume flow.

Doppler measurements have been performed in order to assess a variety of normal and pathological conditions, thereby using two approaches: calculating volume flow or describing the flow velocity waveform by an index. Although volume flow measurements would provide us with much of the desired information, their reliability does not allow us to seriously accept the results as the ultimate truth as will be discussed below in chapter 2.1.1. The second approach, describing the flow velocity waveform by an index appears to be a more reliable method. However, the question arises as to whether these indices reflect important (patho)physiological changes in human fetal hemodynamics, thereby putting emphasis on the pathological condition "intrauterine growth retardation". This will be discussed in chapter 2.1.2.

2.1.1 *Volume flow measurements.*

In human fetal studies, volume flow (Q in cm^3/s) is usually calculated by the simplified formula $Q = (v \times A /\cos\alpha)$, whereby v (cm /s) is the time-average mean velocity or mean temporal velocity, usually determined over one cardiac cycle for calculation of cardiac stroke volume or over one minute for calculation of volume flow per minute in peripheral vessels (Fig 1). A is the cross sectional area in cm^2 and α is the angle between the interrogating Doppler beam and the direction of the moving blood. Sometimes, a correction factor C is introduced, changing the formula into $Q = C \times (v_{tmv} \times A /\cos\alpha)$. C is a constant depending on the shape of the velocity profile. When one assumes that in a vessel a certain

Figure 1. Parameters calculated from the maximal and mean arterial flow velocity waveform.
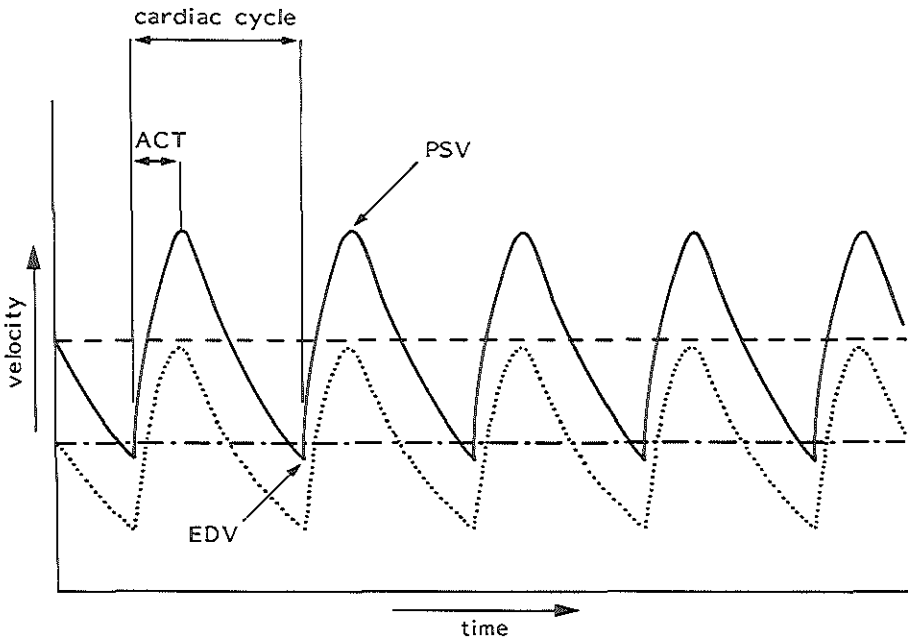
ACT, acceleration time; EDV, end-diastolic velocity; PSV, peak systolic velocity.
line ————— maximal velocity (v_{tmv}).
line — — — time-average maximal velocity (v_{tmv} or AV).
line ...... space average velocity or mean velocity
= the velocity of a flat profile that produces the same volumetric flow rate in a vessel (Hatle and Angelsen, 1985).
line — . — . mean temporal velocity or time-average mean velocity
= space average velocity averaged over time.
position of line ...... depends on frequency or velocity spectrum.

velocity profile exists, the time-average maximal velocity (v_{tmv}) will be multiplied by the factor C belonging to this profile. Both continuous wave and pulsed mode Doppler ultrasound are used. Whereas pulsed wave mode allows depth selection, in continuous wave mode one is able to register high velocities without aliasing.
    Inherent to volume flow calculations are the following assumptions:
a. Blood flow is parallel to the axis of the vessel;
b. An approximation of the angle of insonation can be made;
c. Information about the velocity profile of the vessel of interest is available;
d. The mean temporal velocity or time-average mean velocity can be determined;
e. The mean cross sectional area during the cardiac cycle can be computed;

The reliability of volume flow measurements depends on the degree in which the above mentioned assumptions will be met in the actual measurements. The validity of these assumptions may give rise to difficulties. Crucial factors are:

a. Helical flow

In adult vessels blood flow is helical with the exception of the distal common carotid artery and the mid to distal superficial femoral artery where blood flow is para-axial (Ku and Giddons, 1983; Beach, 1987). Helical flow velocities are assumed to exist in the human fetus. If in the vessel of interest helical flow velocities do exist, the Doppler spectrum will contain helical flow velocities. Correcting the helical flow velocities for the angle of insonation will result in a considerable overestimation (Beach, 1987) if this vessel has not been insonated parallel to the axis of the vessel. Of interest is that in a recent study of aortic root flow velocity profiles in adults, the observers were confronted with the observation that the direction of the blood velocity vector was not parallel to the long axis of the aorta, but skewed towards the right anterior wall (Mathison et al., 1988).

b. Determination of the insonation angle

Errors in the estimation of flow velocity may occur when Doppler velocity measurements are not being made parallel to the bloodstream due to difficulties in assessing the degree of the angle between the Doppler beam and the direction of the blood flow. The accuracy of the determination of the insonation angle will depend on the skill of the sonographer, the imaging qualities of the equipment, fetal activity and fetal age.

c. Flat and parabolic flow velocity profiles

Based on laminar flow, the velocity profile varies (i) with the type of the vessel, i.e. from flat in the cardiac outflow tract to parabolic in peripheral vessels with a low resistance (fig 2), and ii) with the progress of the cardiac cycle (Fig 3). For example in the cardiac outflow tract and the descending aorta the velocity profile varies from flat during the acceleration phase to flat-parabolic during the deceleration phase (Hatle and Angelsen, 1985).

The shape of the velocity profile has implications for defining space average velocity over the arterial cross section at a certain point during the cardiac cycle. It has been suggested that in the presence of a flat profile (i.e. plug flow) the space average velocity will equal the maximal velocity, whereas in case of a flat-parabolic profile the computation becomes much more complicated. For a parabolic profile the space average velocity will be half the maximal velocity.

At cardiac level, both in the adult and fetus, volume flow measurements are performed with the assumption that a flat profile exists. This is based on the fact that the ventricular outflow tract is a converging flow cross section which together with the acceleration flattens the profile (Hatle and Angelsen, 1985). Furthermore, the flat profile conveys in a parabolic profile downstream a vessel
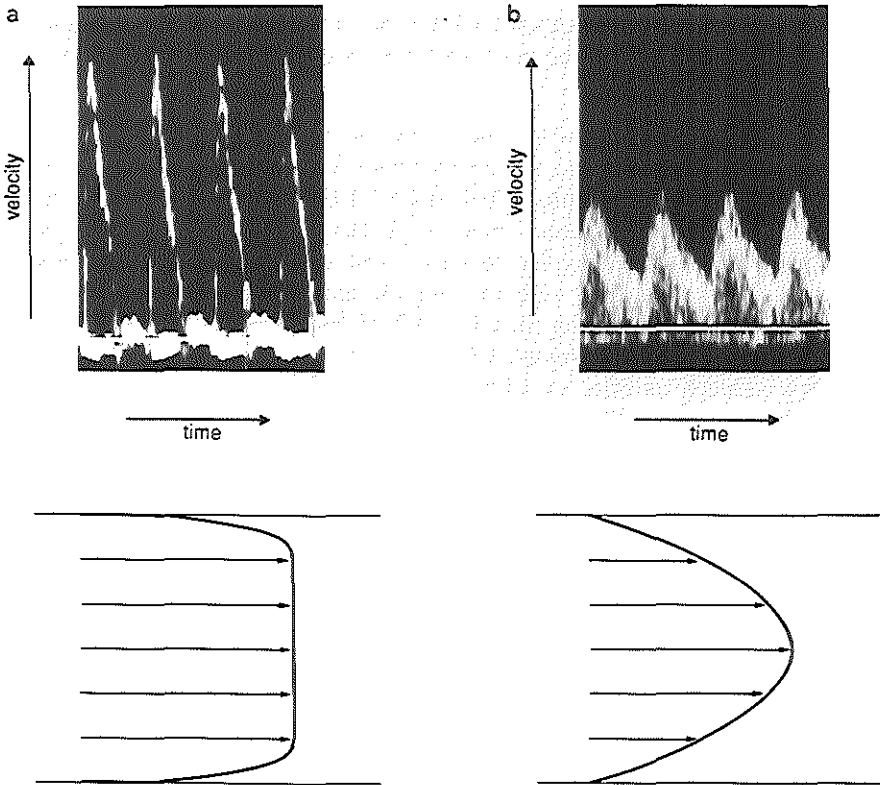
Figure 2. Respective assumed flat and parabolic flow profile in the ascending aorta (a) and umbilical artery (b).

at a certain point during its traject determined by the inlet length. The inlet length of the ascending aorta is longer than the aorta itself, so that one considers the outflow tract profile as being flat (McDonald, 1974). Also the narrow flow velocity envelope obtained at fetal cardiac level, i.e. less than 10 % of the Doppler frequency shift, suggests a flat velocity profile (Meijboom, 1985). Although several reports both from animal and human studies have confirmed this assumption (Clark and Schultz, 1973; Gill et al., 1973; Farthing and Peronneau, 1979; Fisher et al., 1983; Paulsen and Hasenkam, 1983; Lucas et al., 1984; Berman and Alverson, 1985), a recent study showed that in adults the velocity profile of the ascending aorta about one cm from the aortic valve was not flat but parabolic (Mathison et al., 1988).

It is known that the aortic arch will skew the profile, whereby the highest velocities exists in the inner part of the arch (Peronneau, 1974). Moreover, human
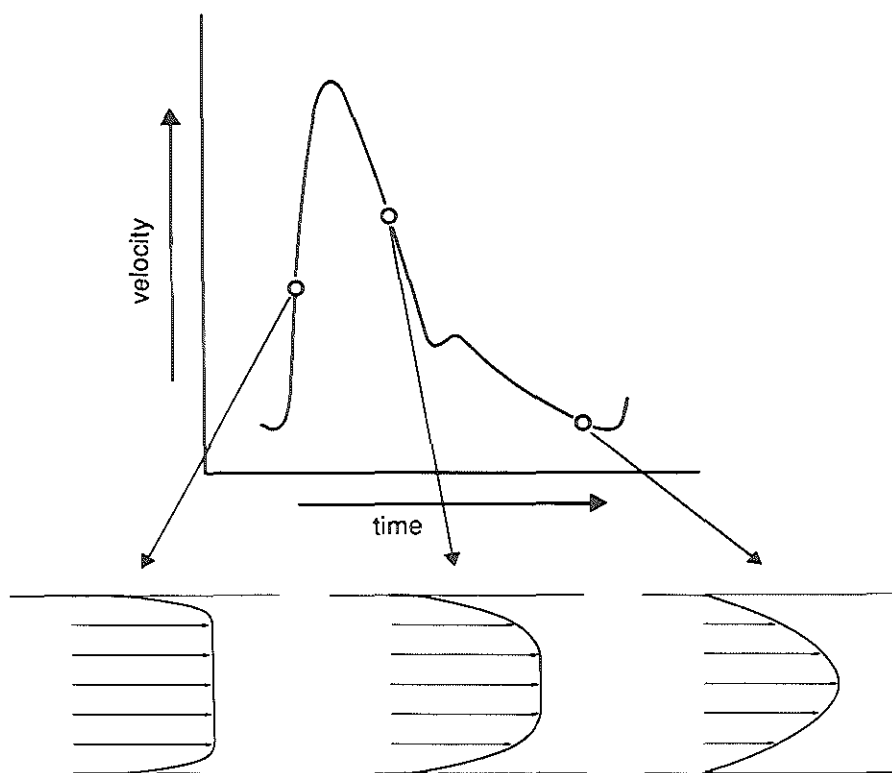
Figure 3. Assumed changes in arterial velocity profile during the cardiac cycle in the fetal descending aorta.

and animal data suggest a certain skewness of the velocity profile at the aortic root (Clark and Schultz, 1973; Farthing and Peronneau, 1979; Paulsen and Hasenkam, 1983; Mathison et al., 1988). This emphasizes the fact that when the three-dimensional shape of the flow velocity profile is not a symmetrical one, the flow velocity waveform which is obtained depends on the two-dimensional plane in which Doppler measurements are performed.

d. Mean temporal velocity

The mean temporal velocity is the space average velocity or mean Doppler shift averaged over a certain period, for instance the cardiac cycle. When the mean Doppler shift is automatically computed by the Doppler device, considerable overestimation may occur depending on the high pass filter used (Eik-Nes et al., 1984). Uniform insonation of the vessel is required in order to include all velocity components, particulary when insonating a vessel in which the velocity profile is not flat but for instance flat-parabolic. Since the beam width of most

Doppler devices used in prenatal settings is about 2-3 mm, uniform insonation can only be accomplished when using a large sample volume and insonating under a certain angle resulting in coverage of the entire vessel lumen by the sample volume (Gill, 1985). Depending on the position of the sample volume either the maximal velocities in the centre of the lumen or the more laterally existing lower velocities will be measured. As a result, the observed velocity distribution may differ from the true distribution across the lumen. This implies that if the velocity profile in the ascending aorta is not as flat as has been supposed, the commonly used small ultrasonic Doppler beam introduces errors in both maximal and mean velocity estimation. Finally, the Doppler spectrum obtained by fast Fourier transformation (FFT) spectral analysis does not necessarily equal the velocity profile. The spectrum is blurred by the transit time broadening effect and the limited data collection time due to the pulsatile character of flow (Hatle and Angelsen, 1985; Burns, 1987).

e. Vessel size

Fetal vessels are small and visualization of the vessel walls depends on several factors such as the resolution of the ultrasound equipment, amount of amniotic fluid and distance between transducer and vessel of interest. Even a small error in calliper positioning may result in a considerable error in vessel diameter estimation. M-mode recordings may provide more reliable results, but any error in diameter estimation will be squared when computing the volume flow (Struijk et al., 1985; De Vore et al., 1987). Furthermore, during the cardiac cycle the diameter of the vessel will change. An effort has been made to overcome this by using a time-distance recorder for continuous recording of the vessel diameter changes (Lindström et al., 1977; Eik-Nes et al., 1982; Struijk et al., 1985). Synchronizing blood flow velocity waveforms and diameter changes is possible by using the ECG (Lingman et al., 1986) or the first derivative of flow velocity (Tonge et al., 1987).

A large standard deviation in volume measurements was revealed by Erskine and Ritchie (1985), as would be expected in view of the above mentioned difficulties relating volume flow measurements. They enumerated their results of umbilical vein and aortic volume blood flow measurements, and those reported by others.

Volume flow studies performed at cardiac level reveal differences in estimated ventricular output. The results of Kenny et al. (1986) and Allan et al. (1987) are in close agreement. They estimated combined cardiac output of the human fetus at 450 ml /min /kg (end third trimester) and 420-450 ml /min /kg (26-32 wks of gestation), respectively. In contrast, De Smedt et al. (1987) calculated combined cardiac output at 553 ± 153 ml /min /kg. Lower values were reported by Maulik et al. (1984): right ventricular cardiac output varied between 128 and 239 ml /min /kg in six fetuses at 28-36 weeks of gestation. Cardiac output per kg bodyweight is assumed to be more or less constant throughout pregnancy

(Allan et al., 1987; De Smedt et al., 1987). Despite the differences in estimated cardiac output, all Doppler studies performed at cardiac level support the presence of right ventricular dominance in the human fetus (Huhta et al., 1985; Kenny et al., 1986; Reed et al., 1986;1987a; Allan et al., 1987; De Smedt et al., 1987) with the right cardiac ventricular output being larger than the left cardiac ventricular output.

Variation in calculated stroke volume (ml) and cardiac output (ml /min) or standardized cardiac output (ml /min /kg) between individuals increases considerably during the last part of gestation. Possible explanations are the increase in vessel diameter and thus area estimation and an increase in biological variation between individuals. Except for the study of De Smedt et al. (1987) no standard deviations are given.

It can be concluded that there are many pitfalls. It is obvious that one is faced with an almost impossible task to meet all the conditions in the actual measurements to make the aforementioned assumptions valid. Therefore volume flow measurements have been abandoned by most centres.

2.1.2 *Describing the flow velocity waveform by an index.*

One can distinguish the indices or parameters describing the flow velocity waveform at cardiac level (chapter 2.1.2.1) from those describing the flow velocity waveform in peripheral vessels (chapter 2.1.2.2). When considering Doppler flow measurements at cardiac level, attention is focused on reports regarding the ascending aorta and pulmonary artery.

2.1.2.1 *Cardiac level*

Commonly used parameters to describe the velocity profile in the cardiac outflow tract, ductus arteriosus and at atrioventricular valve level are: peak systolic velocity (PSV), time-average maximal velocity (usually denoted as time-average velocity) (AV), flow velocity integral (FVI) and acceleration time (ACT). The acceleration time is the time interval between the onset of the waveform and the peak systolic velocity (fig 1).

These cardiac parameters are calculated from flow velocity waveforms obtained parallel to the direction of the blood flow, or otherwise from angle-corrected flow velocity waveforms.

Like volume flow, all these parameters represent absolute values. Consequently, some of the assumptions inherent to volume flow calculations enumerated in chapter 2.1.1 will also apply to the calculation of these parameters.

Problems associated with the reliability of cardiac indices are limited to the first three assumptions pointed out in chapter 2.1.1. In addition to the information on the velocity profile of the vessel (assumption c), it must be stressed that the three-dimensional shape of the profile has certain implications for defining the aforementioned parameters. Several studies have shown that the plane and the site of the flow velocity waveform recording in the adult pulmonary artery

were important factors in determining the peak systolic velocity and acceleration time and therefore also the time-average maximal velocity (Lighty et al., 1986; Panidis et al., 1986; Shaffer et al., 1990). Another problem arising from this approach is that no consensus exists on the definition of some of these parameters. Differences exist between centres in defining the peak systolic velocity and thus the time-average maximal velocity; either the middle or the top of the darkest part of the flow velocity envelope is traced in determining the maximal velocity. In spite of this, the documented peak systolic velocities in the pulmonary artery and ascending aorta have been reported to be in the same range (Huhta, 1985; Kenny et al., 1986; Reed et al., 1986; Allan et al., 1987; Hata et al., 1987).

Information on the variability of fetal cardiac parameters is limited to the reproducibility of tracing flow velocity waveforms (Kenny et al., 1986). Regarding the reproducibility of cardiac parameters in adults, changes in ascending aortic parameters of 10 to 17% (Gardin et al., 1984) and 20 to 25% (Hatle and Angelsen, 1982) have been established, which may reflect true hemodynamic changes. Gardin et al. (1984) reported data obtained by the same technician and observer. They found a large interobserver variability for the acceleration time. Moreover, pathological situations are known to increase the variability of cardiac indices in the adult. Applying these results to the human fetus, one might expect an even larger variation in fetal cardiac parameters and thus stroke volume due to movements of the fetus, vessel size, and inaccessibility of the vessels. As mentioned afore, the documented maximal velocities in the pulmonary artery and ascending aorta are in the same range. However, a blurred image is presented as no graphic presentation of individual measurements is depicted (except for the study of Hata et al., 1987) and no standard deviations are given.

Various factors affect the cardiac velocity profile and thus cardiac velocity parameters. Among these are preload, afterload (including pressure and peripheral resistance), the intrinsic contractile properties of the left and right ventricle and fetal heart rate. Also stroke volume may affect velocity parameters as has been demonstrated in adults (Gisvold and Brubakk, 1982).

a. Stroke volume

PSV and AV correlate to some extent with the mean temporal velocity. Additionally, they all depict a linear increase with advancing gestational age (Kenny et al., 1986; Allan et al., 1987; Hata et al., 1987). In contrast, the valve orifice areas increase in an exponential manner. Consequently, volume flow will increase exponentially as shown by the aforementioned reports on fetal cardiac output. Whereas one will expect PSV and AV to reflect volume flow, the nature of the relation will not be a linear one. Allan et al. (1987) stated that the increase in volume flow with increasing gestational age is accounted for by the increase in size of the valve orifices.

Assuming the vessel diameter will not change during a single study period, then PSV and AV (and FVI) may reflect volume flow. However, variations between individuals and partly unknown changes in vessel diameter under pathologically

circumstances do not allow us to accept changes in volume flow as an explanation for changes in these cardiac parameters.

b. Fetal heart rate

Kenny et al. (1987) assessed by means of acoustic stimulation the effect of increasing fetal heart rate within the physiological range on ventricular stroke volume (SV) and cardiac output. SV was calculated as the product of vessel area and flow velocity integral (FVI). Whereas a significant decrease in FVI and thus SV in the presence of a decreased ventricular end-diastolic area was found, fetal cardiac output per minute was not affected. In a longitudinal study, van der Mooren et al. (1991) found no significant correlation between fetal heart rate (range 112-166 bpm) and PSV, AV or ACT, when interpolating data for each patient to 30 weeks of gestation. These results indicate that although fetal heart rate affects the cardiac parameters, further studies are required to assess whether it is necessary or possible to introduce a correction factor for fetal heart rate changes.

c. Loading conditions

The effect of loading conditions on flow velocity profiles in the cardiac outflow tract is one of the major topics in adult cardiology (Gardin, 1989). In the adult, changes in afterload and preload have their effect upon the velocity profile. For the pulmonary artery an increase in afterload (i.e. pulmonary artery pressure) was associated with a decrease in acceleration time (Kitabatake et al., 1983; Dabestani et al., 1987). For the ascending aorta an inverse relation was found between afterload (expressed as left ventricular peak wall stress) on the one hand and peak systolic velocity and acceleration velocity on the other hand (Bedotto et al., 1989; Harrison et al., 1989). Increasing the preload in the ascending aorta resulted in increases in peak systolic velocity and acceleration velocity (Bedotto et al., 1989).

It is assumed that in the human fetus like in the fetal lamb the left and right ventricle are subjected to the same filling pressures as a result of the presence of the foramen ovale and therefore to the same preload (Rudolph, 1985). In a post-mortem study on human fetal hearts, no differences were established in right and left ventricular growth, weight and morphometry with advancing gestational age (St.John Sutton et al., 1984a). These findings confirmed the results from M-mode studies by Allan et al. (1982), Wladimiroff et al. (1982) and St.John Sutton et al. (1984b) assessing cardiac dimensions. In contrast Sahn (1980) reported a left-right ventricular diameter difference in favour of the right ventricle. It was concluded that the right and left ventricle may be regarded as two muscular pumps working in parallel with the same preload and similar afterload. This was based on the assumption that the ductus arteriosus has a similar diameter to that of the pulmonary trunk and ascending aorta, and afterload is a major determinant of ventricular muscle mass (St.John Sutton et al., 1984b). However, Angelini et al. (1988) showed that in the second trimester human fetus the isthmus was larger than the ductus arteriosus according to post-mortem

measurements, but were similar in size when measured echographically. From post-mortem and echocardiographic measurements the mean ratio of the ductus arteriosus to the ascending aorta was 0.51 and 0.70, respectively.

Human Doppler studies have not clarified the effect of loading conditions upon the flow velocity profile. Assuming the acceleration time will reflect afterload the results are partly contradictory. Both Machado et al. (1987) and van der Mooren et al. (1991) found the acceleration time in the pulmonary artery flow velocity waveform to be shorter than in the ascending aorta. However, whereas in one study (Machado et al., 1987) acceleration time in both outflow tract vessels remained unchanged with advancing gestational age, in the other study (van der Mooren et al., 1991) an increase in acceleration time for both arteries was observed with advancing gestational age, whereby the difference in acceleration time gradually became smaller. It is suggested that the shorter acceleration time in the pulmonary artery reflects the higher afterload to the right ventricle as expressed by raised pulmonary pressure (Machado et al., 1987) or raised peripheral resistance (van der Mooren et al., 1991) compared to the ascending aorta.

The first report relating changes in cardiac indices to intrauterine growth retardation originated from Reed et al. (1987b). Doppler blood flow velocities at cardiac level were documented in fourteen fetuses with absent diastolic flow velocities in the umbilical artery, the majority of them being growth-retarded. Peak systolic velocities at atrioventricular valves and at the semilunar valves were significantly lower compared to controls, except for the peak systolic velocity in the pulmonary artery which was not significantly decreased. Noteworthy is the increased volume flow across the tricuspid and pulmonary valves when correcting for fetal weight. In contrast, Al-Ghazali et al. (1989) found a decreased volume flow through the right heart expressed as percentage of combined cardiac output in asymmetrical growth retardation, whereas in symmetrical growth retardation this was not essentially different from normal fetuses. Moreover, in asymmetrical growth retardation, the peak systolic velocities at the pulmonary artery and not the peak systolic velocities at the ascending aorta were significantly decreased as compared to controls.

2.1.2.2 *Peripheral level*

Commonly used indices for describing the flow velocity waveform of the fetal peripheral vessels are the Pulsatility Index or PI (Gosling and King, 1975), Resistance Index or RI or Pourcelot Index (Pourcelot, 1974), D/S ratio (Trudinger et al., 1985b) and A/B or S/D ratio (FitzGerald and Drumm 1977; Stuart et al., 1980).

These indices are calculated as follows (fig 1):

$$PI = \frac{PSV - MV}{Vtmv} \qquad A/B = \frac{PSV}{EDV}$$

$$RI = \frac{PSV - EDV}{PSV} \qquad D/S = \frac{EDV}{PSV}$$

(PSV = peak systolic velocity; EDV = end-diastolic velocity; MV = minimal velocity; Vtmv = time-average maximal velocity). The peak, time-average maximal, minimal or end-diastolic velocity in these formulas can be replaced by the peak, time-average maximal, minimal or end-diastolic frequency.

Some reports have appeared regarding the best choice of index (Thompson et al., 1986;1988; Pearce et al., 1988; Hoskins et al., 1989; Adamson et al., 1990). The A/B ratio differs from the other parameters in that it has no normal distribution (Thompson et al. 1986;1988; Pearce et al., 1988).

As most of the peripheral fetal vessels have a curved or tortuous course, the angle-independent character of these indices is of particular importance. By dividing two velocities or frequencies in the formula, the cosine of the angle in the denominator and numerator cancel each other out. For obtaining good quality signals the angle of insonation should be 60 degrees or less.

Although one is apparently not confronted with any of the aforementioned assumptions described in chapter 2.1.1, one may question the validity of peripheral measurements. This is particulary so for the uteroplacental arteries in which one can never be totally certain of obtaining the same vessel as on the previous occasion (Campbell and Cohen-Overbeek, 1987). Reproducibility of Doppler measurements has been studied in peripheral vessels, particularly in the umbilical cord, descending aorta and uteroplacental arteries.

There is general agreement on the validity and reproducibility of umbilical artery measurements. The various studies report a good reproducibility for this particular vessel (Reuwer et al., 1984; Schulman et al., 1984; Nienhuis et al., 1988; Gudmundsson et al., 1990). However, one cannot simply compare results between different centres due to differences in Doppler analyzing systems (Ruissen et al., 1988). In a prospective study assessing the components contributing to the variance of umbilical artery Doppler measurements, 10%-14% and 5%-9% of total variance was attributable to interobserver and intraobserver variability, respectively; 33%-46% and 15-18% of total variance was attributable to gestational age and fetal heart rate, respectively (Maulik et al., 1989).

Campbell and Cohen-Overbeek (1987) compared the results of several reports on uteroplacental artery reproducibility. Due to various approaches in statistical analyzing between studies, different conclusions were drawn with respect to inter and intraobserver variability. The major problem seems to be the wide variation of uteroplacental artery flow velocity waveforms within the same patient (Gudmundsson et al., 1990).

For the descending aorta, Pearce et al. (1988) found no significant differences in measurements performed by different observers. According to Nienhuis et al. (1988) there is no systematic examiner effect, however the reliability of descending aorta flow velocity waveforms is limited by the strong decline in PI values along the short descent of the aorta.

Whether or not the site of measurement in the umbilical artery affects the pulsatility of the flow velocity waveform remains controversial. In contrast to other reports (Mehalek et al., 1988; Abramowicz et al., 1989; Maulik et al. 1989), Ruissen et al. (1991) and Trudinger et al. (1985a) did not find a significant effect of the site of measurement on the pulsatility of the umbilical artery. Information about daily variation of flow velocity waveforms in peripheral vessels is limited to one report assessing the umbilical and uteroplacental arteries. It was concluded that after 30 weeks of gestation the magnitude of daily variation in pulsatility in both arteries is acceptable for clinical and research applications (Hastie et al., 1988).

The peripheral indices are determined by cardiac contraction force, vessel compliance, blood viscosity, and in particular downstream impedance.

As the microvascular structure of the placenta in pregnancies complicated by growth retardation differs from normal pregnancy (Brosens et al., 1977), this might imply that in the growth-retarded fetus changes in downstream impedance occur and therefore the indices in certain peripheral vessels will differ.

Giles et al. (1985) found that in the human fetus an increase in placental resistance as expressed by the (lower) number of small arteries or arterioles was associated with an increase in S/D ratio in the umbilical artery. The pregnancies with a low vessel count were complicated by intrauterine growth retardation. McCowan et al. (1987) and Bracero et al. (1989) confirmed this relation between placental changes and umbilical artery pulsatility. Fok et al. (1990) found a significant correlation between the resistance index in the umbilical artery and the percentage of abnormal arterial vessels in the placenta. These measurements were performed in normal and growth-retarded pregnancies. However, a selection in resistance index between the two groups had been taken place.

Analysis of the umbilical artery flow velocity waveform was shown to be more sensitive and with a higher positive predictive value than the measurement of umbilical venous volume blood flow in the detection of the small-for-gestational age fetus (Giles et al., 1986). These early studies point at the potential value of peripheral Doppler indices in predicting and assessing IUGR.

Studies performed in fetal lamb have shed some light on the significance of these indices relative to changes in downstream impedance. At the same time these studies question a direct relationship between changes in peripheral indices and placental pathology; a complexity of various factors working in parallel or opposite directions is presented.

Embolization of the umbilical placental circulation of fetal lamb, thereby increasing the peripheral vascular resistance, is associated with an increase in RI, S/D, and PI and a decrease in D/S in the umbilical artery (Trudinger et al., 1987; Adamson et al., 1990; Morrow et al., 1989a) and an increase in PI in the descending aorta (Noordam et al., 1987). Trudinger et al. (1987), however, reported a time delay between changes in waveform pulsatility and changes in peripheral resistance. Adamson et al. (1990) also calculated cotyledon vascular

resistance which was increased. The relationship between the indices and cotyledon resistance could be described by a linear correlation for the D /S ratio, RI and PI, and by a non-linear correlation for the S /D ratio in the umbilical artery. In addition, Muijsers et al. (1991) found a linear correlation between umbilical PI and umbilical vascular resistance after selective umbilical embolization.

Increasing the resistance of the umbilical cord by infusion of angiotensin II does not affect the shape of umbilical waveform and therefore not the PI (Adamson et al., 1990). Cotyledon resistance was not affected by angiotensin II; the decrease in placental perfusion was established by the decrease in umbilical blood flow. From this study it was concluded that the above mentioned indices were not indicators of changes in umbilical blood flow.

Vasoactive substances (including angiotensin II) do affect the resistance of the umbilical artery, but do not significantly increase the pulsatility of the umbilical artery waveform (Irion and Clark, 1990a). Huisseling et al. (1990) found both increases and decreases in umbilical PI and non-significant increases in cotyledon resistance after angiotensin administration. Based on the results of a umbilical cord compression study by Abitbol et al. (1989), it was concluded that the flow velocity waveform responded to both changes in resistance and to fetal cardiac output. Also, Irion and Clark (1990a) found a relation between umbilical artery blood flow and umbilical vascular resistance on the one hand and S /D ratio on the other hand in fetal lamb. However, this relationship vanished when administering vasoactive agents except for a thromboxane A2 sympaticomimetic agent (Irion and Clark, 1990b). This agent is capable of increasing cotyledon resistance (Trudinger et al., 1989).

Based on human data there is no close correlation between the pulsatility of the umbilical artery and umbilical vein flow with advancing gestational age (St.John Sutton, 1990).

Van Vugt et al. (1988) studied the effect of partial occlusion of the umbilical vein upon the flow velocity waveforms in the umbilical arteries. During umbilical vein occlusion of 40% and more, no significant change in placental vascular resistance was observed. It was concluded that the observed increase in the PI in the umbilical artery was very likely caused by the increased placental outflow pressure (measured in a major cotyledon vein).

Hasaart et al. (1989) pointed out the differences between umbilical venous and arterial occlusion. Umbilical artery occlusion produces a small increase in uterine blood flow and no changes in uterine vascular resistance. Umbilical vein occlusion produces a decrease in uterine blood flow and an increase in uterine vascular resistance.

These studies indicate that still much controversy exists about the weight of various causal factors affecting peripheral indices. Although the peripheral indices of the umbilical artery and descending aorta are affected by increases in peripheral vascular resistance, chronic animal studies are needed to assess the relationship between changes in peripheral vascular resistance resulting in intrauterine growth

retardation and changes in flow pulsatility of the fetal arterial vessels.

Finally, the peripheral indices may also be affected by fetal variables, such as fetal heart rate, fetal breathing movements (Maršál et al., 1984) and fetal behavioural states (van Eyck et al., 1985;1987).

The effect of heart rate upon the flow velocity waveforms has been studied extensively. Increasing the heart rate will raise the end-diastolic velocity and as a result lower the PI. Most of the studies report a significant correlation between fetal heart rate and the peripheral indices in the umbilical artery, descending aorta, internal carotid artery and uteroplacental artery (Mulders et al., 1986;1988; Mires et al., 1987; van den Wijngaard et al., 1988; Brar et al., 1989; Kofinas et al., 1989; Newnham et al., 1990). Thompson et al. (1986) and Lingman and Maršál (1986) found no such relationship. Different opinions exist as to whether the flow velocity waveforms should be corrected for heart rate or not. However, according to Hoskins et al. (1989) it is not possible to correct for short-term changes in waveform length in individual patients as changes in waveform shape occur independent of the waveform length. This is in agreement with the study by Morrow et al. (1989b), who assessed the effect of spontaneous accelerations of fetal heart rate on the S/D ratio within individuals: a rise was observed in six out of 20 cases in S/D ratio of the umbilical artery. Noteworthy is that the degree of fetal heart rate dependency of the peripheral indices varies with the type of vessel studied and the level of peripheral resistance (van den Wijngaard et al., 1988). Fetal heart rate dependency however, is not affected by gestational age (Newnham et al., 1990). These results indicate that one cannot simply correct for fetal heart rate. Most reports point out that the effect of fetal heart rate variations is within the physiological range and are therefore not clinically significant.

It can be concluded that even if one should be able to overcome all the difficulties mentioned in paragraph 2.1.1., one is faced with considerable inter and intra-individual variations in flow velocity waveforms. This seems to be particulary so for Doppler measurements performed at cardiac level. Clinical application may be limited due to the dynamic character of cardiovascular performance. Whereas considerable information on human fetal cardiovascular dynamics has been collected using Doppler techniques, its application in clinical practice still needs to be further clarified.

2.2. Animal studies.

Much of today's knowledge about fetal hemodynamics has been derived from animal studies. The exploration of the fetal circulation started with the development of human interest in medical science from the early Greeks on (Haynes, 1987). Following the introduction of animal experimental research (Barcroft et al., 1933; Barron, 1947; Ramsey, 1949; Reynolds, 1949a;1949b; Dawes et al., 1953;1954), it was not until the sixties that the first experiments were taking

place involving chronic instrumentation (Meschia et al., 1965). The use of radionuclide-labelled microspheres made it possible to study the distribution of blood flow and measure cardiac output in a chronic preparation in utero (Rudolph and Heymann, 1967). Also, electro-magnetic flow transducers were introduced (Campbell et al., 1967; Berman et al., 1975).

Nowadays one can look back at a diversity of studies assessing the fetal hormonal, neurological and cardiovascular developmental changes and responses to stress. It is obvious that one cannot simply extrapolate conclusions drawn from animal experiments to the human fetus, but it may add to a better understanding of the normal fetal circulation and its reactions to stress.

Regarding the results of these studies one has to bear in mind the following remarks: 1) the O_2 dissociation curve differs for the different species; 2) any pharmacological agent used may have its effect on the cardiovascular system (Rudolph et al., 1981); 3) sheep studies are usually performed in fetuses older than 110 days of gestation (0.7 gestation); 4) exteriorization of the fetus will affect the cardiovascular system (Heymann and Rudolph, 1967); 5) the percentage of cardiac output received by the head is significantly lower in non-primate species, (Rudolph et al., 1971); 6) placental morphology differs from the human (Dawes, 1968); 7) intrauterine growth retardation (IUGR) is a chronic condition, whereas most animal studies involve acute experiments.

In understanding the pathophysiological mechanisms operating in IUGR, experiments assessing the fetal response to hypoxia are of interest, because the chronically impaired placental function as a cause of IUGR leads to the assumption that severe IUGR is associated with fetal hypoxia (Sheppard and Bonnar 1976; De Wolf et al., 1980).

Results from both human fetal and animal studies support this assumption: Soothill et al. (1987) showed by means of cordocentesis that some fetuses that are small-for-gestational age (SGA) are chronically hypoxic and acidotic. SGA fetuses have a significantly lower umbilical venous and arterial pO_2 and pH than appropriate-for-gestational age (AGA) fetuses (Nicolaides et al., 1989). In particular, the combination of SGA and absent end-diastolic velocities in the umbilical artery may result in findings of low pO_2 levels (Nicolaides et al., 1988). IUGR resulting from embolization of the uterine vascular bed in the fetal lamb is associated with a decrease in fetal pO_2 in the last half of the observation period, the mean study period being 29 days (Creasy et al., 1972).

In the vast majority of studies the fetal lamb was used in assessing the fetal response to hypoxia. Several study designs have been used to induce a hypoxic state, among which are cord compression (Itskovitz et al., 1983), maternal hypoxemia (Cohn et al., 1974), embolization of the peripheral circulation (Creasy et al., 1972) and occluding arteries supplying the uterus (Gu et al., 1985).

There is a striking difference between the fetal response to cord compression and the response to maternal hypoxemia. Compression of the umbilical cord increases umbilical placental vascular resistance with no significant change in total fetal body vascular resistance. This implies an increase in blood flow to

the carcass (Itskovitz et al., 1987). Maternal hypoxemia, however, increases fetal body vascular resistance with no significant change in umbilical placental vascular resistance (Cohn et al., 1974; Rudolph, 1984). In the growth-retarded human fetus both the resistance at fetal trunk and the umbilical placental vascular resistance are increased as indicated by Doppler measurements (Griffin et al., 1984; Giles et al., 1985; Trudinger et al., 1985a; Schulman, 1987; Stewart et al., 1990). Nevertheless during both modes of stress a redistribution of cardiac output and blood flow takes place, favouring the central nervous system, heart and adrenal glands (Cohn et al., 1974; Itskovitz et al., 1987; Peeters et al., 1979; Sheldon et al., 1979). Fetal heart rate decreases and arterial pressure increases. Besides increasing the blood flow to organs as a compensating mechanism to maintain oxygen delivery, in some organs oxygen extraction is increased, like in the fetal intestine (Edelstone and Holzman, 1982; Itskovitz et al., 1983) and in the cerebral hemispheres of the immature fetal lamb (Gleason et al., 1990).

A significant decrease in fetal cardiac output occurs in the presence of acidemia (Cohn et al., 1974) or when a 50% reduction of umbilical venous return has been established (Itskovitz et al., 1987). Under these circumstances the redistribution of cardiac output is preserved (Richardson et al., 1989; Block et al., 1990). With the development of metabolic acidemia cerebral fractional oxygen extraction is increased. However, with progressive metabolic acidemia a dramatic decrease in cerebral oxygen consumption is observed suggesting decompensation (Richardson et al., 1989; Rurak et al., 1990).

Information about the mechanisms involved in the fetal cardiovascular responses to hypoxic stress is limited (Hanson, 1988). According to Rudolph et al. (1981), local effects of hypoxemia and acidemia, reflex regulation of baro and chemoreceptor and hormonal regulation may play a role. Reflex bradycardia (after approximately 110 days gestation) developing during hypoxia is abolished by denervation of the arterial chemoreceptors and baroreceptors (Itskovitz and Rudolph, 1982). Denervation of the peripheral chemoreceptors (sino-aortic) does not completely abolish the increased blood flow to the brain, heart and adrenal glands during maternal hypoxemia (Jansen et al., 1989). Therefore, it was suggested that during moderate hypoxemia both the aortic and carotid bodies including an additional mechanism are involved in redistributing fetal blood flow. The aforementioned studies have been performed after 110 days of gestation in fetal lambs.

Of interest is that there are preferential pathways of venous blood in order to guarantee supply of oxygen enriched blood to the heart and brain (Edelstone et al., 1980; Reuss et al., 1981). During cord compression the proportion of umbilical venous blood through the ductus venosus is enhanced at the expense of the right lobe of the liver. Contradictory results have been published about the changes in the proportion of umbilical venous flow shunted through the ductus venosus during maternal hypoxemia (Behrman et al., 1970; Brinkman et al.; 1970; Edelstone et al., 1980; Reuss and Rudolph 1980). The study of

Behrman et al. (1970) and Brinkman et al. (1970) were performed in exteriorized animals. Edelstone et al. (1980) and Reuss and Rudolph (1980) found a small increase in ductus venosus flow during maternal hypoxemia. Of interest is that in the study by Reuss and Rudolph (1980) umbilical venous return was maintained but the proportion of umbilical venous blood flow passing through the ductus venosus and contributing to the cardiac output was significantly increased. It is suggested that the ductus venosus plays a passive role in this process (Rudolph et al., 1981).

The above mentioned results are obtained from acute studies, whereas IUGR is a chronic condition. Few studies have observed the fetal lamb under chronic conditions. The initially raised blood pressure returns to control values, but the haematocrit and haemoglobin content depict a gradual increase (Creasy et al., 1972; Kitanaka et al., 1989). Chronic hypoxemia resulting in growth retardation is associated with a higher brain and heart to bodyweight ratio, a normal fetoplacental bloodvolume per kilogram bodyweight and normal heart rate and cardiac output compared to the control group (Creasy et al., 1972; Goetzman et al., 1984). Despite the significantly lower oxygen delivery, total oxygen consumption is maintained (Goetzman et al., 1984). Although umbilical blood flow is maintained, it represents a smaller percentage of cardiac output (Goetzman et al., 1984).

Recent studies have emphasized the diverse "appearances" of experimentally induced intrauterine growth retardation. There are differences between the circulatory adaptations in moderately and severely growth-retarded fetal lambs. Fetal growth retardation was established by umbilical placental and uteroplacental embolization, resulting in a 20% and 30% decrease in fetal bodyweight, respectively, depending on the severity of embolization. These studies were performed in fetal lambs after 110 days of gestation. Although a 33% decrease in placental blood flow and a 39% decrease in fetal arterial oxygen content was established, no redistribution of blood flow was observed in the moderately growth-retarded fetal lamb in contrast to the severely growth-retarded fetal lamb. However, superimposed hypoxemia resulted in a redistribution of cardiac output and blood flow not essentially different from the response of normo-oxygenated fetal lambs to hypoxemia (Block et al., 1989). The severely growth-retarded fetal lambs showed a redistribution of cardiac output and blood flow prior to superimposing hypoxemia. This response was even more marked during supe- rimposed hypoxemia (Block et al., 1984), whereby the already reduced percentage of cardiac output to the placenta was maintained. These studies stress the capacity of the fetal lamb to sustain chronic fetal hypoxemia, without the necessity of redistributing cardiac output like in severe fetal growth retardation. Other mechanisms, like lowering its growth rate as suggested by Block et al. (1989), are sufficient to maintain oxidative metabolism.

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Chapter 3

Recording techniques and reproducibility of fetal cardiac flow velocity waveforms.

Introductory remarks.

The vast majority of data dealing with blood flow velocity waveforms in IUGR originate from angle-independent recording in the umbilical artery, descending aorta, intracranial, renal, iliac and femoral arteries. A relatively small number of papers has appeared on cardiac flow velocity waveform recordings in IUGR. The position of the cardiac structures and outflow tract vessels usually allows angle-dependent waveform recording with interrogation angles below 10 degrees. Instead of pulsatility index calculations, absolute velocities, in particular the peak systolic, end-diastolic and time-average velocity as well as the acceleration time can be calculated. No data are available on the reproducibility of these parameters originating from the cardiac outflow tract vessels. Information on this is essential for a correct interpretation of outflow tract data under physiological and pathophysiological circumstances.

In this chapter, the recording technique and reproducibility of waveforms obtained from the ascending aorta, pulmonary artery and ductus arteriosus in normal fetuses in the second half of pregnancy will be presented.

3.1 Doppler flow velocity waveforms in the fetal cardiac outflow tract; reproducibility of waveform recording and analysis

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Abstract

Reproducibility of flow velocity waveform recording and analysis was studied at fetal cardiac level (ductus arteriosus, pulmonary artery and ascending aorta) in 42 normal pregnancies. The flow velocity parameters studied were the peak

duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter at 14-22 weeks.

A combined mechanical sector and pulsed/continuous Doppler system (Diasonics CV 400, Diasonics Inc., Mulpikas, CA) with a carrier frequency of 3.5 (real-time) and 3.0 MHz (Doppler) was used. The sector scanner operates at power outputs of less than 100 mW/cm² spatial peak-temporal average in both imaging and Doppler modes according to the manufacturer's specifications. The frequency analysis device of the Diasonics CV 400 is a fast Fourier transformer spectrum analyzer. The data collection time (fast Fourier transit time, FFT) of this spectrum analyzer is 20 ms.

All Doppler studies were performed with the patient in the semirecumbent position and during periods of fetal apnoea, because high-amplitude fetal breathing movements modulate blood flow velocity waveforms (Maršál et al., 1984). Measurements were made irrespective of fetal activity or heart rate accelerations. All measurements were performed by one investigator (I.A.L.G). Doppler measurements were performed in the ascending aorta, pulmonary artery and ductus arteriosus. Two-dimensional real-time imaging was necessary to position correctly the Doppler sample volume in the vessel of interest. The correct position of the sample volume was verified after each Doppler measurement. Flow velocity waveforms from the ascending aorta, pulmonary artery and ductus arteriosus were obtained from the five-chamber view (Kenny et al., 1986), the conventional short axis view (Kenny et al., 1986) and the ductal plane (Huhta et al., 1987), respectively. Pulsed Doppler was used for flow velocity waveform recording in the ascending aorta and pulmonary artery. A sample volume length of 0.3 cm was used. The sample volume was placed immediately distal to the semilunar valves to obtain flow velocity waveforms with a narrow Doppler spectrum envelope reflecting the flat velocity profile existing in the great vessels. Continuous wave Doppler was used for flow velocity waveform recording in the ductus arteriosus. The high velocities registered in this vessel require a continuous Doppler system as this is not subject to frequency aliasing. Recordings were only accepted if the angle between the interrogating Doppler beam and the direction of the blood flow was estimated at 15 degrees or less. No angle correction was used. For all vessels studied, peak systolic velocity (PSV in cm/s), acceleration time (ACT in ms), acceleration velocity (ACV in m/s²), average velocity (AV in cm/s) and flow velocity integral (FVI in cm) were determined. An average of four consecutive flow velocity waveforms of similar appearance and high signal-noise ratio was used to establish each value. All Doppler waveforms were recorded on videotape. From this tape, hardcopies were made, consisting of four to five flow velocity waveforms (depending on fetal heart rate), that is, two seconds of recording. A flow velocity waveform with a period time of 400 ms will therefore measure 26.5 mm on the X axis of the hardcopy. For measurements performed in the ascending aorta and pulmonary artery, a velocity of 50 cm/s corresponded with 5 cm on the Y axis of the hardcopy, whereas for the ductus arteriosus this corresponded with 2.5 cm on the Y axis

of the hardcopy. An IBM compatible microcomputer (Olivetti M24, Olivetti BV, Leiden, The Netherlands) linked to a graphics tablet (MM 1201, Summagraphics) was used for analysis of the Doppler recordings on the hardcopies. Resolution of the graphics tablet was .05 mm. The analyzing program uses 400 datapoints to describe the four waveforms on one hardcopy. Resolution of the analyzing programme was .325 mm for the X axis and .5 mm for the Y axis of the hardcopy. Flow velocity waveform analysis consisted of tracing the outer border of the densest part of the Doppler spectrum envelope of each waveform with a cursor and defining the onset, maximum and end of the waveform. PSV (cm/s) was defined by the top of the densest part of the Doppler spectrum envelope. ACT (ms) was defined as the time interval between the onset of the waveform and the peak systolic velocity. The datapoints between 10% and 90% of the ascending limb of the curve were used to construct a regression line and thus estimate the ACV (m/s^2). AV (cm/s) was calculated by dividing the sum of velocities over one period time by the number of datapoints. The FVI (cm) was obtained by multiplying the average velocity with the period time.

Reproducibility study.

In each patient, Doppler recordings were performed twice in all three cardiac vessels, at times t_1 and t_2. The time delay between the two measurements was approximately 15 minutes. Of each recording, two hardcopies were made. These hardcopies did not reveal the identity or gestational age of the patient nor the date or time of recording. After collecting the hardcopies, they were shuffled in a random order and analyzed. Both Doppler recording and waveform analysis was performed by the same investigator (I.A.L.G). Statistical analysis consisted of Nested Analysis of Variance to separate the total variation in components due to differences between patients, differences between repeated tests within patients and differences between analyses of hardcopies. Linear relations between variables were assessed using Pearson's correlations. Other methods used are given in the text. Statistical significance was set at P=.05 (two-sided).

Results

Unacceptable flow velocity waveforms were obtained in one patient (34 weeks of gestation) due to severe obesity, leaving data from 41 patients for further analysis. Acceptable paired recordings of the first Doppler measurement at t_1 and second Doppler measurement at t_2 were obtained from the ductus arteriosus in 26 patients, from the pulmonary artery in 29 patients and from the ascending aorta in 31 patients. If one of the two Doppler recordings was unsuccessful in a particular vessel, the entire recording was omitted from further analysis, since it did not contribute to the analysis of variation between tests. The success rate in obtaining paired recordings in the ductus arteriosus correlated positively with the success rate in collecting paired recordings in the pulmonary artery,

Table 1.
Standard deviations (coefficients of variation between parentheses) derived from Analysis of Variance.

	PSV(cm/s)	ACT(ms)	ACV(m/s^2)	AV(cm/s)	FVI(cm)
DA					
σ_p	16.7 (18%)	11.2 (20%)	5.6 (27%)	5.5 (16%)	2.9 (20%)
σ_t	3.2 (3%)	9.7 (17%)	2.9 (14%)	2.0 (6%)	1.0 (7%)
σ_c	0.9 (1%)	2.9 (5%)	3.9 (19%)	0.6 (2%)	0.3 (2%)
PA					
σ_p	9.4 (17%)	7.8 (15%)	2.7 (20%)	3.1 (18%)	1.4 (19%)
σ_t	1.2 (2%)	5.1 (10%)	0.0 (0%)	0.8 (5%)	0.3 (4%)
σ_c	0.6 (1%)	4.3 (8%)	4.9 (36%)	0.4 (2%)	0.2 (3%)
AO					
σ_p	8.8 (12%)	5.2 (10%)	3.5 (17%)	2.8 (14%)	1.2 (14%)
σ_t	1.8 (2%)	5.3 (11%)	2.8 (14%)	0.9 (4%)	0.4 (5%)
σ_c	0.6 (1%)	4.2 (8%)	6.6 (32%)	0.6 (3%)	0.2 (2%)

DA=ductus arteriosus; PA=pulmonary artery; AO=ascending aorta; PSV=peak systolic velocity; ACT=acceleration time; ACV=acceleration velocity; AV=average velocity; FVI=flow velocity integral.
σ_p corresponds to differences between patients, σ_t to differences between repeated tests (time delay 15 min) within patients and σ_c to differences between readings of hardcopies.

and vice versa (Fisher's exact test: p<.05). The success rate in obtaining acceptable paired recordings at t_1 and t_2 from the ductus arteriosus, pulmonary artery or ascending aorta did not correlate with gestational age. Table 1 gives standard deviations corresponding to the three sources of variation for each vessel. The best results, both for the variation in hardcopy analyses as well as the variation between repeated tests, were obtained for the peak systolic velocity. Figure 1 shows test results for this parameter for individual patients.

For all Doppler parameters, the standard deviations corresponding to the two consecutive tests did not significantly correlate with gestational age. The difference in fetal heart rate between the two consecutive tests was less than 11 bpm in 90% of tests (range 0-19, median 4 bpm). In reanalysing the data, confining the analysis to tests in which the fetal heart rate differed ≤10 bpm, the resulting components of variance did not appreciably differ from those given in table 1.

Discussion

The present results show that analyses from hardcopies can be performed with a high reproducibility for the parameters PSV, AV and FVI. Also, the variation between repeated tests at an interval of 15 minutes is small for these parameters. The reproducibility of hardcopy analyses for ACT appears smaller as compared
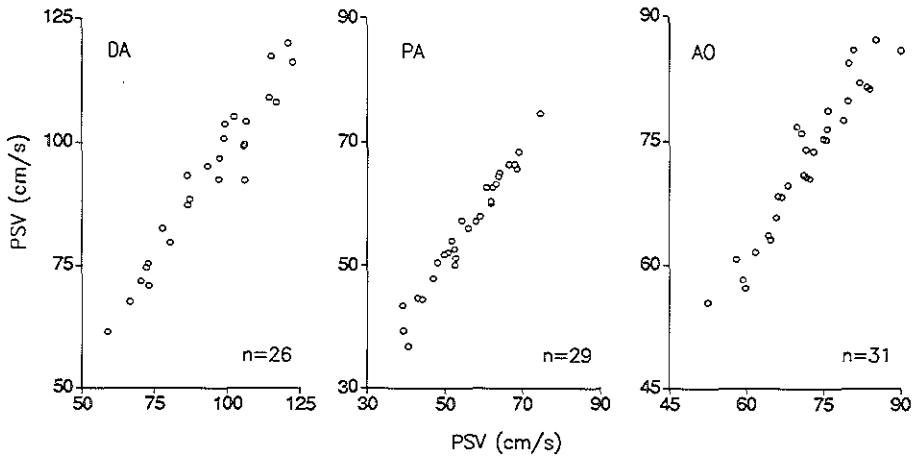
Figure 1. Peak systolic velocity (PSV) at second test (vertical) versus first test (horizontal) for DA, PA and AO. Plotted data are the means of two hardcopy readings. DA=ductus arteriosus; PA=pulmonary artery; AO=ascending aorta.

with PSV, AV and FVI, but still seems acceptable. The variation between tests, however, is considerable. This is particulary so for the flow velocity waveform recordings from the ductus arteriosus. A poor reproducibility was established for the ACV from the analyses of hardcopies, while there were also considerable differences between repeated tests for the ascending aorta and ductus arteriosus. Variation due to the tracing hardcopies is unacceptably large for using this cardiac parameter in describing cardiac dynamics under any circumstances. An acceptable explanation for this poor reproducibility is found in the steepness of the ascending limb of the flow velocity waveform. The ascending limb is too steep to be traced accurately by hand. Another explanation is found in the relatively long FFT of 20 ms. The fast Fourier transformer spectrum analyzer tests for a set of frequencies and displays the intensities of each of the frequencies present as a function of time in the form of a spectral waveform (Beach, 1987). For each spectral estimate, a short portion of the signal is used. The longer the data collection time (FFT) used for spectral estimate, the larger the inaccuracies in estimation of velocity changes. The relatively long data collection time (FFT) of 20 ms limits accurate estimation of high-rate velocity changes by the spectrum analyzer.

The moderate reproducibility for the ACT can also be partly explained by the fast Fourier transit time (FFT): Suspicion arises as to whether the FFT enables accurate determination of the ACT because the FFT of 20 ms is large compared to the mean ACT of about 40 ms. Moreover, several reports have appeared on the effect of sample volume positioning regarding the ACT (Panidis et al., 1986; Shaffer et al., 1990).

In the present study, the sample volume was always placed immediately distal to the valves. No considerable differences in fetal heart rate were observed between the two consecutive tests. The large between-tests variation which was observed for some parameters is therefore not largely affected by variations in heart rate. Reanalysis of data, leaving out those with a difference of more than 10 bpm between the two tests, confirmed this finding. The standard deviation corresponding to the two consecutive measurements does not significantly increase or decrease with gestational age, indicating gestational age independency in our reproducibility study.

The positive correlation between the ductus arteriosus and the pulmonary artery in successfully obtaining an acceptable Doppler measurement is not surprising. Due to the close anatomical relationship between the two vessels, only a minor change in scanning plane is necessary to obtain a flow velocity waveform from the other vessel.

It can be concluded that at the level of the fetal cardiac outflow tract, a high reproducibility in determining PSV, AV and FVI can be achieved, indicating that these cardiac parameters can be used for assessing cardiac function. Whereas a moderate reproducibility was achieved for the ACT in the ascending aorta and the pulmonary artery, the reproducibility in the ACT of the ductus arteriosus and the ACV in all vessels studied was poor.

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Chapter 4

Changes in fetal cardiac and extra-cardiac flow velocity waveforms relative to fetal growth retardation.

Introductory remarks.

Insight into the processes of cardiovascular adaptation in the growth-retarded fetus can only be obtained if not only placental perfusion, but also blood supply at other major organ levels is studied. It was because of Doppler measurements in the fetal internal carotid artery that the brain-sparing effect was first demonstrated in the growth-retarded human fetus (Wladimiroff et al., 1986). Later, this process of preferential brain-sparing was also shown in the middle cerebral artery (Woo et al., 1987) and anterior cerebral artery (Arbeille et al., 1987). Flow velocity recording in all four major intracranial vessels in normal and growth-retarded fetuses is the subject of chapter 4.1.

Since IUGR due to reduced placental perfusion is associated with reduced resistance at fetal trunk and lower extremity level as well as fetal brain-sparing, one may expect altered cardiac performance under these circumstances. It should be realized that cardiac performance is determined by a variety of factors such as preload, afterload, heart rate and contraction force. Doppler ultrasound will not allow differentiation between all these variables. Combined cardiac outflow tract and extra-cardiac waveform analysis should provide a more complete picture of cardiovascular adaption in IUGR. This will be presented in chapter 4.2.

It soon became clear that there is a difference in left and right cardiac ventricular performance in both the normal and growth-retarded fetus. Attention was, therefore, focused on the flow velocity waveforms obtained from the ascending aorta and pulmonary artery in a longitudinal study design during the second half of pregnancy. Data from this study are presented in chapter 4.3.

4.1 Cerebral Doppler ultrasound of the human fetus

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Summary

Maximal flow velocity waveforms were recorded in the internal carotid artery (ICA), middle cerebral artery (MCA), posterior cerebral artery (PCA) and anterior cerebral artery (ACA) in 55 normal pregnancies and 14 complicated by intrauterine growth retardation between 25 and 41 weeks gestation. In normal pregnancy, acceptable flow velocity waveforms were obtained in the ICA in 89%, in the MCA in 91%, in the PCA in 58% and in the ACA in 64%. A decrease in pulsatility was observed in all four intracranial arteries during the latter weeks of gestation. In growth-retarded pregnancies, pulsatility in all vessels was significantly reduced compared with normal pregnancy, suggesting participation of all major intracranial arteries in a brain-sparing effect in the presence of chronic fetal hypoxia.

Introduction

Recently, duplex sonography, a combination of high-resolution real-time and pulse-gated directed Doppler ultrasound, was introduced in the study of blood flow velocity waveforms in the human fetal internal carotid artery (Wladimiroff et al., 1986). Direct evidence for the occurrence of a brain-sparing effect in cases of intrauterine growth retardation (IUGR) due to placental insufficiency was provided (Wladimiroff et al., 1987; Arduini et al., 1987). In contrast to the umbilical artery, however, pulsatility index (PI) calculations in the internal carotid artery exhibited a poor sensitivity in identifying IUGR (Wladimiroff et al., 1988).

The objective of the present study was twofold: first, to study basic flow patterns in the basal cerebral arteries in the healthy human fetus; second, to assess the hemodynamic status of the growth-retarded human fetus.

Materials and Methods

A total of 14 patients with fetal growth retardation was referred to our ultrasound unit between February and July 1987. Gestational age ranged between 27 and 37 weeks. During the same study period 55 pregnant subjects with uncomplicated pregnancies were randomly selected to serve as controls. Here, gestational age varied between 25 and 41 weeks. Each patient was certain of the date of onset of her last menstrual period.

Normal pregnancies were defined by normal fetal biparietal diameter (BPD), head circumference and upper abdominal circumference measurements according to the nomogram by Campbell (1976) and by birth weight between the 10th and 90th percentile for gestational age according to Kloosterman's tables (Kloosterman, 1970) corrected for parity and fetal sex. Intrauterine growth retardation (IUGR) was defined as a growth pattern resulting in a clinical dis-

crepancy of >2 weeks on fundal height on two successive antenatal appoint-
ments, and ultrasound findings of upper abdominal circumference measurements
below the 5th percentile in association with normal or reduced head circumference
measurement. Head to abdominal ratio values were calculated as described by
Campbell and Thoms (1977). IUGR was retrospectively confirmed by the birth
of an infant under the 5th percentile for gestational age according to Kloosterman's
tables (Kloosterman, 1970) corrected for parity and fetal sex.

Of the 14 pregnancies with IUGR, 10 (71%) exhibited an elevated head to
abdominal ratio; 7 (50%) presented with pregnancy-induced hypertension; in
the other seven there was no overt maternal or fetal disease. There were four
perinatal deaths. In the pregnancies with IUGR, the mean lag time between
blood flow velocity recording and delivery was 11 days (range 1-47).

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 basal cerebral arteries.

The maximum flow velocity waveform in the internal carotid artery (ICA)
was obtained at the level of the bifurcation into the middle and anterior cerebral
artery, as described previously (Wladimiroff et al., 1986). The sample volume
was set at 4 mm and the high-pass filter at 100 Hz. A schematic display of
the anatomical location of the basal cerebral arteries (anterior, middle and
posterior arteries) is presented in Figure 1. An axial view of the fetal head
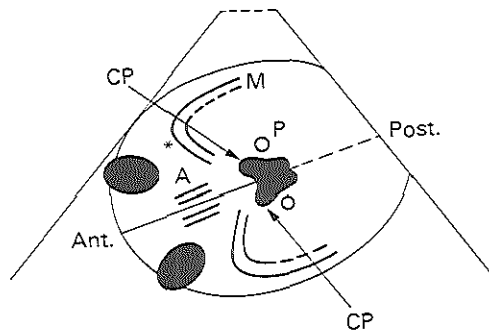
Figure 1. Schematic representation of the ultrasound cross section of the fetal head with the anatomical
location of the anterior (A), middle (M) and posterior (P) cerebral arteries. CP, Cerebral peduncle;
*, position of sample volume for middle cerebral artery measurement.

was obtained at the level of the cerebral peduncles. The arterial pulsations of
the right and left middle cerebral artery (MCA) can be seen running from their
origin of the internal carotid artery into the lateral sulcus over the anterior
perforated substance and disappearing onto the cerebral fossa between the
temporal lobe and insula. The sampling cursor was placed into the pulsating
artery in the lateral sulcus, closest to the Doppler transducer. The posterior cerebral
arteries (PCA) can be seen coursing around the midbrain in the ambient cistern.

Flow velocity recordings were made at the level of the transverse cerebral fissure on the side of the midbrain closest to the Doppler probe. Finally, using the pulsating internal carotid artery as landmark, the sampling cursor was moved anteriorly along the mid-line over a distance of approximately 2 cm. The sample volume was enlarged to 12 mm, thereby allowing the flow velocity waveform of both anterior cerebral arteries (ACA) to be recorded, and thus facilitating the initial identification of flow in these vessels. The sample volume was then reduced to 4 mm to exclude one of the two signals. For all four vessels, the angle between the Doppler interrogation beam and flow direction was always kept below 60 degrees. The degree of pulsatility of the waveform was quantified by calculating the pulsatility index (PI) according to Gosling and King (1975) over at least four consecutive cardiac cycles. All measurements were performed with the woman in the semirecumbent position and during fetal apnoea, since high-amplitude fetal breathing modulates the blood flow velocity waveforms (Maršál et al., 1984).

Statistical analysis included investigation of the relations between the PI values and gestational age by polynomial regression (Deter et al., 1982). The percentage of pregnancies with IUGR that had abnormal PI levels was compared with the corresponding percentage of normal subjects using Fisher's exact test.

Results

Acceptable flow velocity waveforms for PI calculations were obtained in the ICA in 49 (89%), in the MCA in 50 (91%), in the PCA in 32 (58%) and in the ACA in 35 (64%) of the normal subjects. The individual data plots of the PI values from these intracranial vessels are presented in Figures 2 - 5.

Fitting polynomials, it appeared that mean PI values of all four vessels could not be described by linear equation, but that also quadratic components of age were needed (Table 1). For none of the parameters did the cubic component of age reach statistical significance. Normal limits, taken as fitted mean values $\pm$ 2 SD, are presented in Figures 2-5. The standard deviations of the measured values around the fitted curves for PI in the ICA, MCA, PCA and ACA were 0.20, 0.22, 0.19 and 0.14 respectively.

Figures 2-5 also display the data points from the IUGR study. PI values were obtained in the ICA in all 14 pregnancies, in the MCA in 13, in the PCA in eight, and in the ACA in 10. In all four vessels the percentage of IUGR cases with a PI value below the 2 SD cut-off level was significantly ($p < 0.001$) greater than the corresponding percentages for normal subjects. The sensitivity in identifying IUGR at the 2 SD cut-off level was 57% for the ICA, 85% for the MCA, 100% for the PCA and 60% for the ACA.
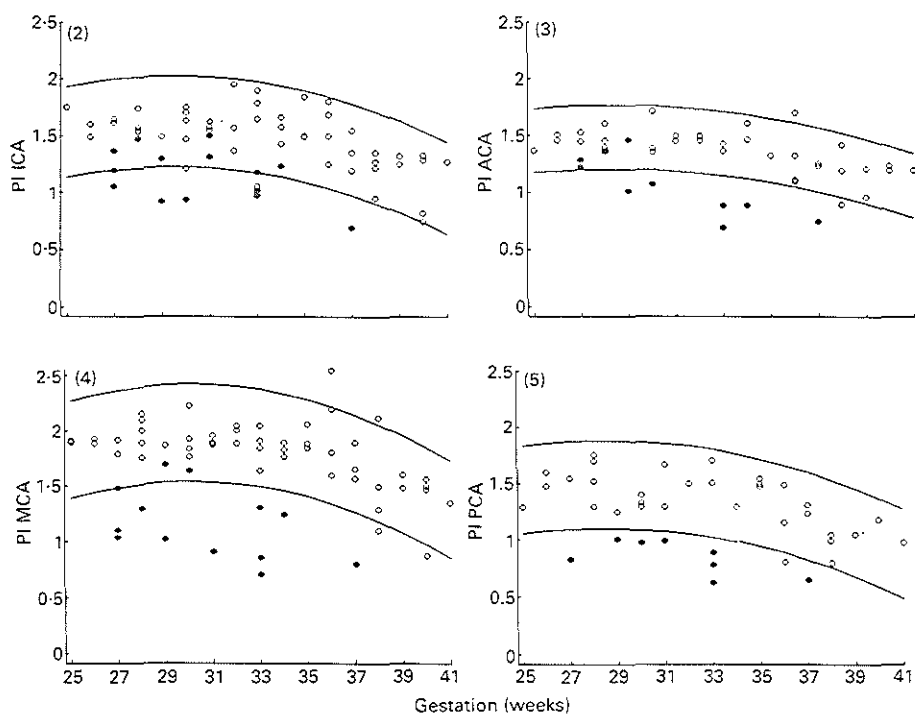
Figures 2-5. Pulsatility index values from the fetal internal carotid artery (PI ICA: Fig.2), anterior cerebral artery (PI ACA: Fig.3), middle cerebral artery (PI MCA: Fig.4) and posterior cerebral artery (PI PCA: Fig.5) for normal pregnancies (open circles) and pregnancies complicated by fetal growth retardation (closed circles) relative to gestational age. Plotted curves represent normal limits ($\pm$ 2 SD).

Table 1.
Results of least-squares quadratic regression of ICA. MCA, PCA and ACA PI values on age.

	Constant	Coefficient of linear term	Coefficient of quadratic term
PI ICA	-2.26 (1.73)	0.26 (0.11)	-0.0044 (0.0016)
PI MCA	-3.44 (1.77)	0.36 (0.11)	-0.0060 (0.0016)
PI PCA	-1.74 (2.00)	0.23 (0.12)	-0.0040 (0.0019)
PI ACA	-0.66 (1.36)	0.15 (0.08)	-0.0027 (0.0013)

Standard errors of regression coefficients are given in parentheses.
PI, Pulsatility index; ICA, internal carotid artery; MCA, middle cerebral artery; PCA, posterior cerebral artery; ACA, anterior cerebral artery.

Discussion

The normal waveform in the fetal internal carotid and basal cerebral arteries in the third trimester of pregnancy always displays forward flow. These large intracranial arteries, therefore, seem to serve a universally low-resistance vascular bed in the human fetal brain. The ICA and MCA always produced the strongest signals, which is reflected in the success rate in obtaining acceptable flow velocity waveforms in these vessels. Signal intensity of the PCA and ACA was frequently weak. Optimal flow velocity waveforms were, therefore, more difficult to obtain. Similar problems were met by Aaslid et al. (1982) who studied Doppler signals from the PCA and ACA in the same scanning plane in healthy adults. In normal pregnancy, PI values in the MCA were markedly higher than in the other intracranial vessels. This is explained by the rapid systolic upstroke in the flow velocity waveform followed by a sharp velocity decline during diastole.

The reduction in PI observed in all four vessels during the latter weeks of normal pregnancy was predominantly determined by an increase in end-diastolic flow velocity. This is in agreement with earlier findings in the fetal ICA (Van den Wijngaard et al., 1988); ACA (Arbeille et al., 1987) and MCA (Woo et al., 1987; Kirkinen et al., 1987). The physiological mechanism responsible for these flow velocity waveform changes is still unknown. Recently a reduction in pO_2 was established in the umbilical artery through cordocentesis during this period of gestation (Soothill et al., 1986). On the basis of this pO_2-reduction, we postulate that the aforementioned increase in end-diastolic flow velocity may reflect a hemodynamic redistribution favouring blood supply to the brain.

In IUGR, there is a marked reduction in PI in the ICA and basal cerebral arteries. These changes are predominantly due to an increase in end-diastolic flow velocity and confirm earlier data (Arduini et al., 1987; Wladimiroff et al., 1987) suggesting a brain-sparing effect in the presence of IUGR. These findings imply that the major intracranial arteries all participate in the circulatory redistribution favouring brain perfusion in the presence of chronic fetal hypoxia. The limited number of IUGR pregnancies in this study does not allow meaningful statistical comparisons regarding sensitivity in detecting IUGR. However, there seems to be an indication, that especially the MCA and PCA, both responsible for blood supply to the brainstem areas, are highly sensitive indicators of fetal compromise. The sensitivity of the PI in the ICA seems to be poor (57%), as has been demonstrated in an earlier study (Wladimiroff et al., 1988) (45%). During the last trimester the fetal head usually faces laterally, and then the optimal vessel for Doppler measurements is the MCA (Kirkinen et al., 1987). The combination of easy accessibility and promising sensitivity warrants a further study of the significance of PI determinations in the MCA for assessing fetal growth retardation.

4.2 Fetal cardiac and peripheral arterial flow velocity waveforms in intrauterine growth retardation.

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Running title: Fetal blood flow in intrauterine growth retardation.

Abstract

Maximum flow velocity waveforms were studied at the cardiac level (ascending aorta, pulmonary artery, ductus arteriosus) and at the peripheral level (fetal internal carotid artery, descending aorta, umbilical artery, maternal uteroplacental artery) in 25 patients with intrauterine growth retardation and 25 normal control subjects matched for gestational age and maternal parity. Gestational age ranged between 27 and 35 weeks (median, 30 weeks). All flow velocity waveforms were obtained with a mechanical sector scanner combined with a pulsed and continuous Doppler system with a carrier frequency of 3.5 and 3.0 MHz. Normal pregnancy was characterized by a low fetal and placental vascular resistance. The peak systolic velocity in the ascending aorta was significantly higher compared with the pulmonary artery. In patients with intrauterine growth retardation, reduced end-diastolic flow velocities were documented in fetal descending aorta, umbilical artery, and maternal uteroplacental artery, reflecting raised umbilical placental and uteroplacental vascular resistances. Raised end-diastolic flow velocities were observed at the cerebral level reflecting reduced cerebral vascular resistance ("brain-sparing" effect). Reduced peak systolic flow velocities documented at the cardiac level may be secondary to reduced volume flow, increased valve or vessel size, or raised afterload. The noninvasive nature of this study did not allow differentiation between these variables.

Mini-abstract

Maximum flow velocity waveforms were recorded at cardiac and peripheral level in 25 cases of intrauterine growth retardation (IUGR) and 25 normal controls matched for gestational age (27 - 35 weeks) and maternal parity. Normal pregnancy was characterized by a low fetoplacental vascular resistance. In IUGR, elevated vascular resistance at fetal trunk and placental level was associated

with reduced cerebral vascular resistance (brain-sparing effect) and reduced peak systolic flow velocity at cardiac outflow tract level.

Key words: Pulsatility index, Peak systolic velocity, Brain-sparing effect, Placental vascular resistance.

Introduction

Previous work on fetal hemodynamic function has centred mainly on the lamb. Two-dimensional real-time and Doppler ultrasound makes possible noninvasive examination of the human fetal cardiovascular system. Doppler studies of the fetal umbilical and maternal uteroplacental artery have been reported to identify fetuses at risk for intrauterine growth retardation (IUGR) and poor fetal outcome (Campbell et al., 1987; Reuwer et al., 1987; Schulman, 1987; Trudinger et al., 1987a). Reduced end-diastolic flow velocities in the fetal umbilical, aortic, and maternal uteroplacental arteries have been associated with increased peripheral vascular resistance, indicating impaired placental perfusion (Griffin et al., 1984; Giles et al., 1985; Schulman, 1987; Trudinger et al., 1987b). However, reports on the effect of this increase in afterload on the fetal heart have been contradictory. Both increased right ventricular cardiac output (Reed et al., 1987a) and decreased (Al-Ghazali et al., 1988) combined ventricular cardiac output have been documented in the absence of end-diastolic flow in the umbilical artery.

The purpose of the present study was twofold: first, to document the changes in cardiac and peripheral arterial blood flow velocity waveforms in the growth-retarded fetus according to a matched controlled study design; second, to relate these flow velocity waveform changes to placental disease.

Materials and Methods

IUGR was diagnosed in 25 singleton pregnancies at 27 - 35 weeks of gestation (median, 30 weeks) when the fetal abdominal circumference was below the fifth percentile for gestational age (Campbell and Wilkins, 1975). The pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter at 14 - 20 weeks. Maternal age ranged from 16 to 44 years (median 27, years). Maternal parity was 0 in 23 patients, one in one patient, and two in the remaining patient. Concomitant complications were pregnancy-induced hypertension in seven patients and preeclampsia in 11 patients. Pregnancy-induced hypertension is defined as a diastolic blood pressure of 90 mm Hg or more in the second half of pregnancy in a previously normotensive woman. In preeclampsia, pregnancy-induced hypertension is accompanied by proteinuria of 300 mg /l or more. In the remaining seven pregnant woman no cause for the IUGR could be established. Twenty-five normal singleton pregnancies with the fetal abdominal circumference between

the fifth and 95th percentile for gestational age served as matched controls. Matching took place with respect to gestational age and maternal parity. Maternal age in the normal group varied between 19 and 39 years (median, 26 years). In the IUGR group, fetal birth weight was below the fifth percentile, and in the normal control group, fetal birth weight was between the 10th and 95th percentile according to Kloosterman's Tables (Kloosterman, 1970) corrected for maternal parity and fetal sex. The study protocol was approved by the Hospital Ethics Committee. All pregnant women consented to participate in the study.

A combined mechanical sector and pulsed-continuous Doppler system (Diasonics CV 400, Diasonics Inc, Mulpikas, California) with a carrier frequency of 3.5 and 3.0 MHz was used. The sector scanner operates at power outputs of less than 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes by manufacturer's specifications. Two-dimensional real-time imaging was needed to position the Doppler sample volume in the region of interest. Maximum flow velocity waveforms were recorded at both cardiac and peripheral levels. Each patient was included in the study only once. Doppler studies were performed by one examiner (I.A.L.G.). At cardiac level, Doppler recordings were produced from the fetal ascending aorta, pulmonary artery, and ductus arteriosus. Flow velocity waveforms from the fetal ascending aorta were obtained from the five-chamber view (figure 1). Fetal pulmonary artery flow velocity waveforms were recorded from the conventional echocardiographic short axis view (figure 1). Doppler sample volumes were placed in the great vessels immediately distal to the semilunar valves (Reed et al., 1987b). Flow velocity waveforms from the fetal ductus arteriosus were obtained from the short axis view distal to the pulmonary artery (Huhta et al., 1987) (continuous Doppler) (Figure 1). The angle between the Doppler cursor and the assumed direction of flow was always 5 degrees. Sample volume length was between 0.1 and 0.3 cm. The correct position of the pulsed Doppler gate was ensured by two-dimensional ultrasound before and after each Doppler tracing was obtained. Peak systolic velocity (cm/sec) was determined in all three cardiac vessels studied.

Peripheral arterial Doppler studies were focused on the maternal uteroplacental artery, the lower thoracic part of the fetal descending aorta and fetal umbilical artery representing the uteroplacental and umbilical placental circulation, and the fetal internal carotid artery representing cerebral blood flow. In each instance, the procedure consisted of location of the vessel of interest followed by recording of the arterial flow velocity waveform. Placing the two-dimensional real-time transducer over the outer margin of the uterus nearest to the placenta, the maternal common iliac artery is visualized where it bifurcates into the external and internal iliac arteries. With the continuous wave Doppler transducer directed more medially, a uteroplacental artery in the lateral uterine wall may be identified (Campbell et al., 1987). Doppler signals from this vessel are in the opposite direction to those from the iliac arteries (Campbell et al., 1987) and were always recorded on the placental side (Figure 2). The flow velocity waveform in the umbilical artery was obtained from a free-floating loop of the umbilical cord
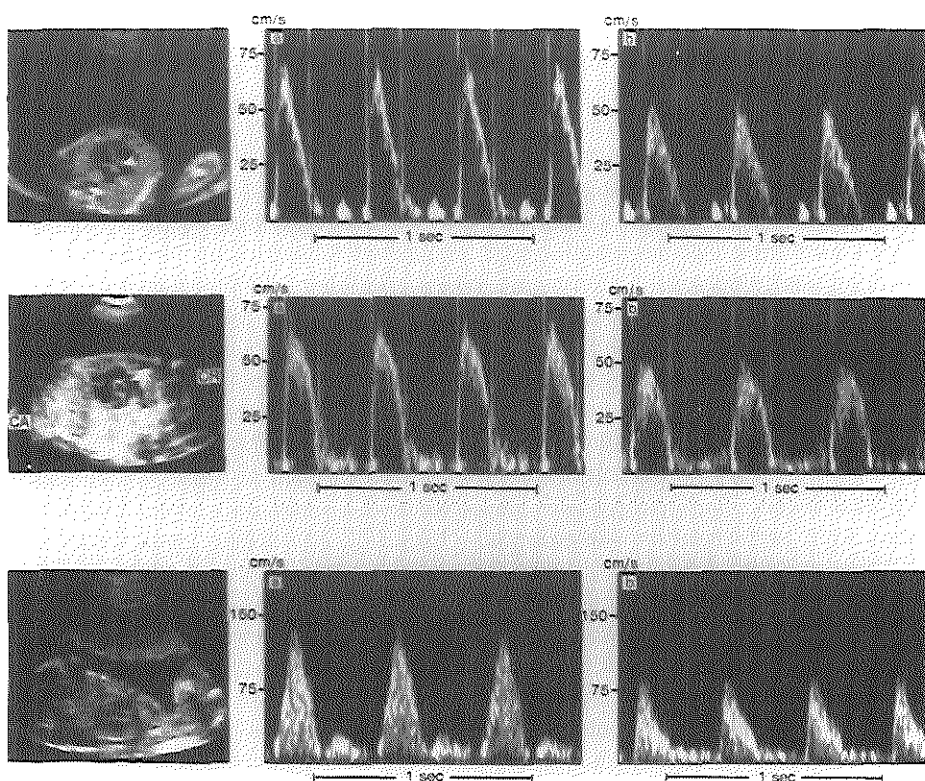
Figure 1. **Top panel:** Two-dimensional five-chamber view of the human fetal heart with Doppler flow velocity waveform tracings from the ascending aorta (see arrow) during normal pregnancy (a) and intrauterine growth retardation (IUGR) (b). **Middle panel:** Two-dimensional short axis and pulmonary arterial view of the human fetal heart with Doppler flow velocity waveform tracings from the pulmonary artery (see arrow) during normal pregnancy (a) and IUGR (b). CR, cranial; CA, caudal. **Bottom panel:** Two-dimensional short axis view of the human fetal heart parallel to the fetal spine with Doppler flow velocity waveform tracings from the ductus arteriosus (see arrow) during normal pregnancy (a) and IUGR (b).

(McCallum et al., 1978) in both the presence of normal and reduced amounts of amniotic fluid (Figure 2). Flow velocity waveforms from the lower thoracic part of the fetal descending aorta were recorded from a sagittal cross section through the fetal trunk, displaying a major section of the fetal spine (Eik-Nes et al., 1980) (Figure 3). Fetal internal carotid artery flow velocity waveforms were documented on a transverse cross section through the lower part of the fetal cerebrum showing a heart-shaped cross section of the brain stem with the anterior lobes representing the pedunculi cerebri (Wladimiroff et al., 1986). Anterior to this heart-shaped structure and, on either side of the mid-line, an oblique cross section of the internal carotid artery as it divides into its middle
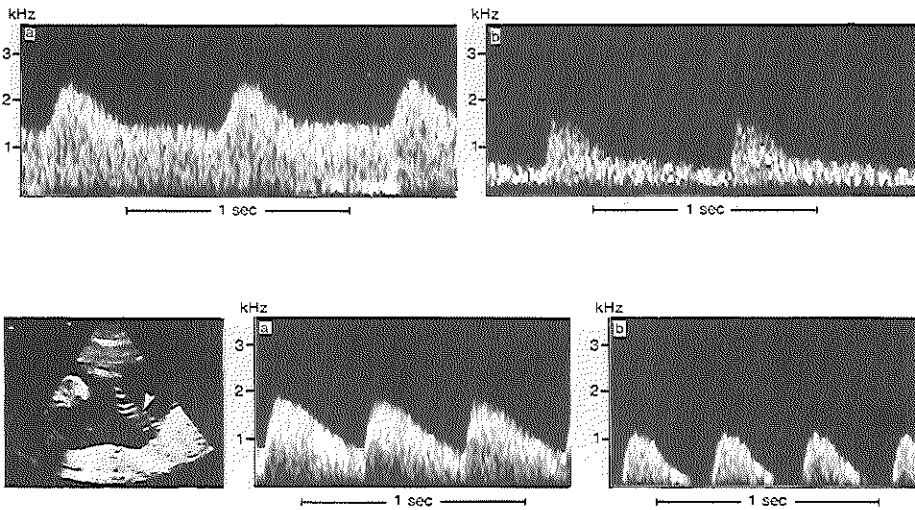
Figure 2. **Top panel:** Doppler flow velocity waveform tracings from a uteroplacental vessel during normal pregnancy (a) and intrauterine growth retardation (IUGR) (b). **Bottom panel:** Two-dimensional transverse cross section of the pregnant uterus with Doppler flow velocity waveform tracings from the umbilical artery (arrow indicates umbilical cord) during normal pregnancy (a) and IUGR (b).

and anterior cerebral branches can be seen (Figure 3). The tortuous or curved course of the maternal uteroplacental, umbilical, and fetal internal carotid artery did not allow positioning of the Doppler cursor parallel to the direction of blood flow, thus rendering impossible an accurate determination of the angle of incidence between flow and the Doppler beam and calculation of absolute velocities. Instead, angle-independent indexes expressing the pulsatility of the arterial flow velocity waveform were calculated. For the maternal uteroplacental artery this was the end-diastolic to peak systolic flow velocity ratio (EDV /PSV ratio), and for the remaining peripheral vessels, this was de pulsatility index (Gosling et al., 1975). The pulsatility index is derived by dividing the difference between peak systolic and end-diastolic velocity by the mean flow velocity over the entire cardiac cycle. Both EDV /PSV ratio and pulsatility index mainly reflect downstream impedance as has been shown in animal (Noordam et al., 1987; Trudinger et al., 1987b) and human studies (Giles et al., 1985). In fetal lambs, embolization of the umbilical placental circulation has been performed to increase placental flow resistance and to observe the effect on the umbilical artery (Trudinger et al., 1987b) and fetal descending aorta flow velocity waveform (Noordam et al., 1987). A reduction in end-diastolic flow velocity was established in both vessels together with a rise in calculated vascular resistance. In human pregnancy, reduced end-diastolic flow velocities in the umbilical artery were associated with a loss of small arteries in the tertiary villi of the placenta.
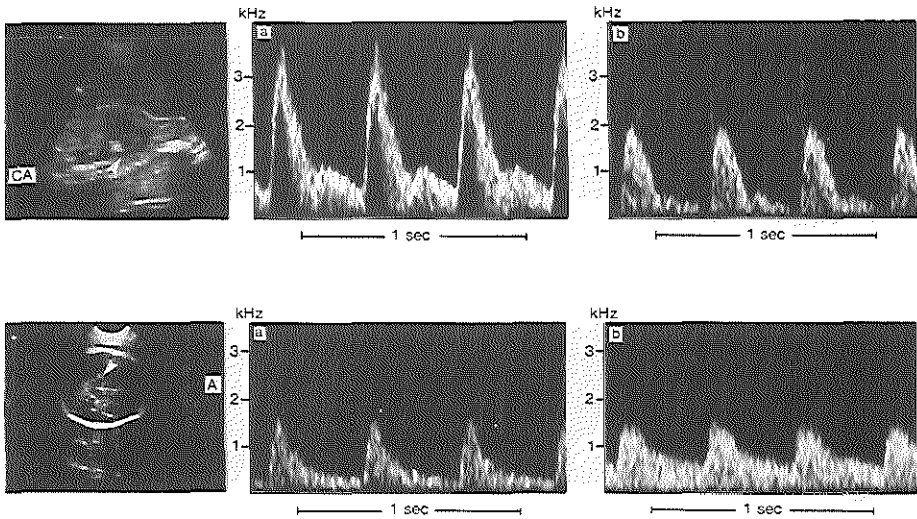
Figure 3. Top panel: Two-dimensional sagittal cross section through the fetal trunk with Doppler flow velocity waveform tracings from the fetal descending aorta (see arrow) during normal pregnancy (a) and intrauterine growth retardation (IUGR) (b). CR. cranial; CA. caudal. Bottom panel: Two-dimensional transverse cross section through the lower part of the fetal brain at the level of the heart-shaped cerebral peduncles (see arrow) with Doppler flow velocity waveform tracings from the internal carotid artery during normal pregnancy (a) and IUGR (b). A. anterior; P. posterior.

All Doppler studies at cardiac and peripheral levels were performed with the patient in the semirecumbent position and during periods of fetal apnoea because high amplitude fetal breathing movements modulate blood flow velocity waveforms (Maršál et al., 1984).

All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24, Olivetti BV, Leiden, The Netherlands) linked to a graphics tablet was used for analysis of the Doppler recordings. An average of four consecutive flow velocity waveforms with the highest velocity and of similar appearance was used to establish each value.

Within the IUGR group, all Doppler flow velocity waveforms were recorded within 14 days of delivery (median, 4 days), thus allowing assessment of the relationship between these flow velocity waveforms and the percentage of placental infarction. For this, the placentas were cut into slices of 0.5 cm each. The number and dimensions of the areas of infarction were defined through macroscopic examination, and the percentage of placental infarction was subsequently calculated.

Statistical analysis of the data consisted of the Wilcoxon Matched-pairs signed-ranks test for comparing the Doppler data from the IUGR patients with data from the matched control subjects. Comparison of the Doppler data from the

IUGR patients with the degree of placental infarction was performed by calculation of the correlation coefficient. Multiple regression was used to simultaneously investigate the relation of the various Doppler measurements with the percentage of placental infarction. Statistical significance was tested at the level of 0.05.

Results

Doppler Data From Patients With Intrauterine Growth Retardation Compared With Normal Control Subjects.

Tables 1 and 2 present the peripheral and cardiac flow velocity waveform values in IUGR patients and normal control subjects. In normal pregnancy, high-forward velocity levels are maintained throughout end-diastole in the maternal uteroplacental artery, umbilical artery, fetal descending aorta, and fetal internal carotid artery. In IUGR, a statistically significant reduction of peak systolic velocity in all three cardiac vessels as well as the pulsatility index from the fetal internal carotid artery and EDV /PSV ratio from the maternal uteroplacental artery was documented. A statistically significant rise was observed for the pulsatility index from the umbilical artery and fetal descending aorta. Six cases of IUGR ended in intrauterine death before 30 weeks of gestation. The flow velocity waveforms from these cases did not significantly differ from those of the surviving IUGR cases of similar gestational age. Both during normal pregnancy and IUGR, the peak systolic velocity in the fetal ascending aorta was significantly higher than that in the pulmonary artery. There was no significant difference in mean fetal heart rate (beats /min) between normal pregnancies (141; range, 123-157) and cases of IUGR (145; range, 125-155).

Doppler Data From Patients With Intrauterine Growth Retardation Relative to Degree of Placental Infarction

The percentage of placental infarction ranged from 0% to 50% (median, 15%). A significantly positive correlation was established between the percentage of placenta infarction and pulsatility index from the fetal descending aorta ($r = +0.53$, $p = 0.02$) and umbilical artery ($r = +0.69$, $p = 0.001$). A significantly negative correlation was present between the percentage of placental infarction and the EDV /PSV ratio in the maternal uteroplacental artery ($r = -0.60$, $p = 0.005$) as well as the peak systolic velocity ($r = -0.49$, $p = 0.03$) in the fetal pulmonary artery.

Multiple regression, also taking into account gestational age, revealed that the strongest correlation with the percentage of placental infarction was displayed by the pulsatility index from the umbilical artery and the EDV /PSV ratio from the maternal uteroplacental artery.

Table 1. Peripheral Flow Velocity Waveform Values in Patients With Intrauterine Growth Retardation and Normal Control Subjects.

	Normal group (n=25)			IUGR group (n=25)			Significance of difference (p)
	Mean	SD	Range	Mean	SD	Range	
EDV/PSV ratio maternal							
Uteroplacental artery	0.65	0.05	0.56-0.74	0.49	0.11	0.25-0.68	<0.001
PI umbilical artery	1.05	0.16	0.74-1.49	2.87	1.48	1.23-7.20	<0.001
PI fetal internal							
Carotid artery	1.66	0.25	1.14-2.43	1.02	0.23	0.59-1.48	<0.001
PI fetal descending aorta	1.65	0.26	1.15-2.05	2.55	0.48	1.67-3.40	<0.001

IUGR, intrauterine growth retardation; EDV/PSV, end-diastolic velocity to peak systolic velocity ratio; PI, pulsatility index.

Table 2. Cardiac Flow Velocity Waveform Values in Patients With Intrauterine Growth Retardation and Normal Control Subjects.

	Normal group (n=25)			IUGR group (n=25)			Significance of difference (p)
	Mean	SD	Range	Mean	SD	Range	
Fetal ascending aorta							
Peak systolic velocity (cm/sec)	70.8	6.3	60.9- 85.9	56.5	7.1	43.1- 70.0	<0.001
Fetal pulmonary artery							
Peak systolic velocity (cm/sec)	60.8	4.7	53.3- 74.7	46.6	5.7	37.3- 55.7	<0.001
Fetal ductus arteriosus*							
Peak systolic velocity (cm/sec)	97.4	11.0	76.7-119.0	83.1	13.1	61.6-118.0	<0.01

* n=23

Discussion

Normal pregnancy is characterized by a low fetal and placental vascular resistance. In the presence of IUGR, there is an elevated pulsatility index in the fetal descending aorta and umbilical artery and a reduced EDV/PSV ratio in the maternal uteroplacental artery resulting from a reduction in end-diastolic flow velocities and reflecting increased umbilical placental and uteroplacental vascular resistance. These data can be viewed as an indication of impaired uteroplacental perfusion (Griffin et al., 1984; Reuwer et al., 1987; Schulman, 1987; Trudinger et al., 1987a). The reduced pulsatility index values in the fetal internal carotid artery suggest reduced cerebral vascular resistance, that is a "brain-sparing" effect as a result of fetal circulatory centralization in the presence of IUGR (Wladimiroff et al., 1986;1987).

At the cardiac level, Doppler flow velocity waveforms have been previously recorded across the atrioventricular valves (Kenny et al., 1986; Reed et al., 1986a;1986b;1987a; De Smedt et al., 1987) and in the outflow tract (Kenny et al., 1986; De Smedt et al., 1987; Al-Ghazali et al., 1988). In the present study, flow velocity waveforms were successfully recorded in the fetal ascending aorta and pulmonary artery in 100% and in the fetal ductus arteriosus in 92% of the IUGR patients.

In normal pregnancy, the mean peak systolic velocity in the ascending aorta and pulmonary artery was not essentially different from that reported by other investigators (Reed et al., 1986a; Huhta et al., 1987). Peak systolic velocities in ductus arteriosus depicted a wide scatter as has been established by other investigators (Huhta et al., 1987; Moise et al., 1988), the mean peak systolic velocity being nearly 100 cm /sec. In IUGR patients, peak systolic flow velocities were markedly reduced in all three cardiac vessels. For the ascending aorta and pulmonary artery, a similar reduction in peak systolic velocity was established.

Peak systolic flow velocity at cardiac valve level is a function of the flow through the valve and cross-sectional area of the valve. Peak systolic flow velocity is influenced by various factors such as preload, afterload (including arterial pressure and vascular resistance), heart rate, and the intrinsic contractile properties of the left and right ventricle. The human fetal model does not allow differentiation between all these factors. One may speculate that the higher peak systolic velocities in the ascending aorta compared to the pulmonary artery observed in normal pregnancy may be due to decreased fetal cerebral vascular resistance (Wladimiroff et al., 1988) with subsequently lower left ventricular afterload. Based on time to peak velocity measurements in the ascending aorta and pulmonary artery (Machado et al., 1987), it has been suggested that in normal human fetuses between 16 and 30 weeks, the mean pressure in the pulmonary artery is higher than that in the ascending aorta, which reflects a difference in resistance between the two circuits. Alternatively, the peak systolic velocity differences observed in our own study may well be determined by the difference in semilunar valve area between the two vessels (Allan et al., 1987).

Several explanations can be offered for the etiology of decreases in peak systolic flow velocity in the cardiac outflow tract in IUGR. Because volume flow is equal to mean velocity multiplied by area and because peak systolic velocity correlates to some extent with mean velocity, a decrease in peak systolic velocity could be secondary to a decrease in volume flow. Peak systolic velocity might also be lowered if the valve of vessel through which blood is flowing increased in size, even if a volume flow were maintained or even increased. Changes in contractile function of the ventricle could also result in changes in peak systolic velocity, although tricuspid valve regurgitation was not observed in any of the IUGR patients. In addition, the afterload that is determined by blood pressure and resistance may play a role. Our Doppler studies at umbilical placental and uteroplacental level suggest an increase in resistance in these locations. However, both volume flow and pressure may change (in parallel or opposite directions) and result in alterations in the Doppler flow velocity waveform. Moreover, the waveform may not change with afterload if other factors change simultaneously. Again, differentiation between these explanations is not possible in the present model.

Within the IUGR group, umbilical artery pulsatility index was positively related and maternal uteroplacental artery EDV /PSV ratio values were negatively related to the degree of placental infarction. This is in support of both fetal lamb data in which reduced end-diastolic flow velocities in the umbilical artery, resulting in raised pulsatility index values were documented after embolization of the umbilical placental circulation (Trudinger et al., 1987b) and human data in which similarly abnormal umbilical artery waveforms were associated with a loss of small arteries in the tertiary villi of the placenta (Giles et al., 1985). The degree of placental infarction exhibited a negative relationship with peak systolic flow velocity in the pulmonary artery, whereas no such a relationship could be shown for the peak systolic flow velocity in the ascending aorta. One can only speculate on the etiology of these conditions. Extensive placental vascular infarction is associated with a significantly raised placental vascular resistance that may result in an increased afterload to both ventricles. The afterload to the left ventricle is not only determined by the vascular resistance at fetal trunk and placental level but also by cerebral vascular resistance, which appears to be reduced (brain-sparing) in IUGR. However, other variables influencing peak systolic velocity may also have played a role in this relation.

Our cardiac flow velocity data do not provide information on cardiac output and therefore do not allow comparison with other cardiac Doppler studies in which volume flow calculations at atrioventricular (Allan et al., 1987; De Smedt et al., 1987; Reed et al., 1987a) and outflow tract (Maulik et al., 1984; Allan et al., 1987; Reed et al., 1987a) level have been performed. Contradictory data have appeared on fetal cardiac output varying from increased right ventricular output (Reed et al., 1987a) to reduced combined output (Al-Ghazali et al., 1988) in the presence of abnormal umbilical artery waveform tracings. Some of this discrepancy may be due to the fact that Reed et al. (1987a) corrected for fetal

weight whereas Al-Ghazali et al. (1988) did not. If fetuses are small for their gestational age, they might have decreased cardiac output for age at the same time that they have increased cardiac output for weight. Moreover, a substantial amount of error is potentially present in the method of calculation of fetal volume flow, particularly in smaller fetuses.

In conclusion, our results show that normal pregnancy is characterized by a low fetal and placental vascular resistance, whereas in IUGR there appears to be a raised resistance at umbilical placental and uteroplacental levels with reduced resistance at cerebral level (brain-sparing effect). The reduced peak systolic flow velocities at cardiac level in IUGR may be secondary to reduced volume flow, increased valve or vessel size or raised afterload. The noninvasive nature of the present model does not allow differentiation between these variables.

4.3 Flow velocity waveforms in the fetal cardiac outflow tract as a measure of fetal well-being in intrauterine growth retardation.

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Running title: Fetal cardiac blood flow and growth retardation.

Abstract

Maximum flow velocity waveforms were recorded in a longitudinal study from the fetal ascending aorta and fetal pulmonary artery in 46 normal pregnancies and, in addition, from the umbilical artery in 21 cases of intrauterine growth retardation between 19 and 33 wk gestation. In normal pregnancy, the mean peak systolic velocity (PSV) in the ascending aorta increased from 49.4 cm/s at 19 wk of gestation to 79.0 cm/s at 33 wk of gestation. The corresponding increase in PSV in the pulmonary artery was from 39.0 to 63.7 cm/s. The ratio for the PSV between the two arteries remained constant (1.25 - 1.29). Mean values of PSV in both arteries were linearly related to gestational age. Normal limits according to age were constructed by establishing the 5th and 95th percentiles. In intrauterine growth retardation, the PSV in the pulmonary artery was decreased ($<$ 5th percentile) in 95% of cases, PSV in the ascending aorta was reduced ($<$ 5th percentile) in only 57%. No relationship was established between PSV in both arteries and the presence or absence of end-diastolic flow velocities in the umbilical artery. The outcome of fetuses with IUGR, as expressed

by Apgar score at 1 min and umbilical cord pH, bears no relationship to the PSV in ascending aorta and pulmonary artery.

Abbreviations

AO, ascending aorta
IUGR, intrauterine growth retardation
PA, pulmonary artery
PSV, peak systolic velocity
SDS, SD score

Introduction

Combined two-dimensional real-time imaging and Doppler facilities give reproducible noninvasive information of fetal cardiac function (Huhta et al., 1985; Reed et al., 1986b; Hata et al., 1987). Flow velocity waveforms have been studied under both normal and pathologic circumstances, in combination with atrioventricular or outflow tract dimensions for calculation of ventricular stroke volume or output (Maulik et al., 1984; Kenny et al., 1986; Allan et al., 1987; De Smedt et al., 1987). However, these calculations are subject to a considerable amount of error due to inaccurate dimension measurements. This is particularly so for smaller fetuses.

The objective of the present study was 3-fold: 1) to establish the distribution of peak systolic velocities in the fetal cardiac outflow tract (ascending aorta and pulmonary artery) during the second half of normal pregnancy; 2) to determine the degree of abnormality of peak systolic velocities in the fetal cardiac outflow tract and its relation to end-diastolic flow velocity in the umbilical artery and birth weight in the presence of IUGR due to impaired placental perfusion; 3) to relate peak systolic velocities in the fetal cardiac outflow tract to fetal well-being as expressed by Apgar score at 1 min and umbilical arterial pH.

Materials and Methods

A total of 46 normal pregnancies and 21 cases of IUGR consented to participate in the study. The study protocol was approved by the Hospital Ethics Committee. Doppler examinations in 46 normal pregnancies were carried out at 3- to 4-wk intervals between 19 and 33 wk gestation. It is in this particular period of pregnancy that the vast majority of IUGR cases are referred to our department.

Normal pregnancy was defined by a normal fetal biparietal diameter and birth weight between the 5th and 95th percentile according to Kloosterman's tables, corrected for maternal parity and fetal sex (Kloosterman, 1970). The pregnancy duration was determined from the last menstrual period and confirmed by

ultrasonic measurements of the biparietal diameter between 14 and 18 wk of gestation. The median maternal age was 27 years (range 19-42 years), the median parity was 0 (range 0-3).

IUGR was defined by: 1) flattening of the fetal growth pattern resulting in a clinical discrepancy of more than 2 weeks on fundal height on two successive appointments, combined with an ultrasound finding of the upper abdominal circumference measurement below the 5th percentile in association with a normal or reduced head circumference measurement (Campbell, 1976) and 2) postnatal confirmation by birth weight below the 5th percentile for gestational age, corrected for maternal parity and fetal sex (Kloosterman, 1970). In 14 of 21 cases of IUGR there was pregnancy-induced hypertension. The lag time between flow measurement and delivery in the 21 cases of IUGR was always less than 14 days (median 3 days). If more than one measurement was made per patient, the measurement nearest to the date of delivery was taken for analysis. Median maternal age was 28 years (range 24 - 37 years), median parity 0 (0 - 3). In 17 subjects, flow velocity waveforms from both ascending aorta and pulmonary artery were related to the Apgar score at 1 min; in 15 subjects also to the umbilical artery pH.

A combined mechanical sector and pulsed Doppler system (Diasonics CV 400, Diasonics Inc., Mulpikas, CA) with a carrier frequency of 3.5 and 3.0 MHz was used for blood flow velocity measurements in the ascending aorta, pulmonary artery and umbilical artery. The sector scanner operates at power outputs less than 100 mW/cm^2 spatial peak/temporal average in both imaging and Doppler modes by manufacturer's specifications. Two-dimensional real-time imaging was used to ensure the correct position of the pulsed Doppler gate both before and after each Doppler tracing was obtained. Maximum flow velocity waveforms from the ascending aorta were recorded from the "five-chamber" view (Fig.1). Maximum flow velocity waveforms from the pulmonary artery were collected from the conventional short axis view (Fig.2). In both vessels, the Doppler sample volume was placed immediately distal to the semilunar valves. The Doppler sample volume length ranged between 0.1 and 0.3 cm. Doppler tracings were accepted when the angle between the Doppler cursor and the assumed direction of flow was 15 degrees or less.

In each vessel the peak systolic velocity (cm/s) was determined and the ratio between both peak systolic velocities was calculated. Peak systolic velocities were measured from the zero-line to the highest point of the Doppler velocity peak. Blood flow velocity measurements in the umbilical artery were only performed in IUGR. In this vessel, attention was focused on the end-diastolic part of the flow velocity waveforms that was classified as present or absent. Doppler studies were performed by one examiner (I.A.L.G.). All flow velocity waveforms were recorded on hardcopies. A microcomputer (Olivetti M24, Olivetti BV, Leiden, The Netherlands) linked to a graphics tablet was used for analysis of the Doppler recordings. The mean value over at least four consecutive flow velocity waveforms of optimal quality represented the peak systolic velocity in a particular pregnancy.
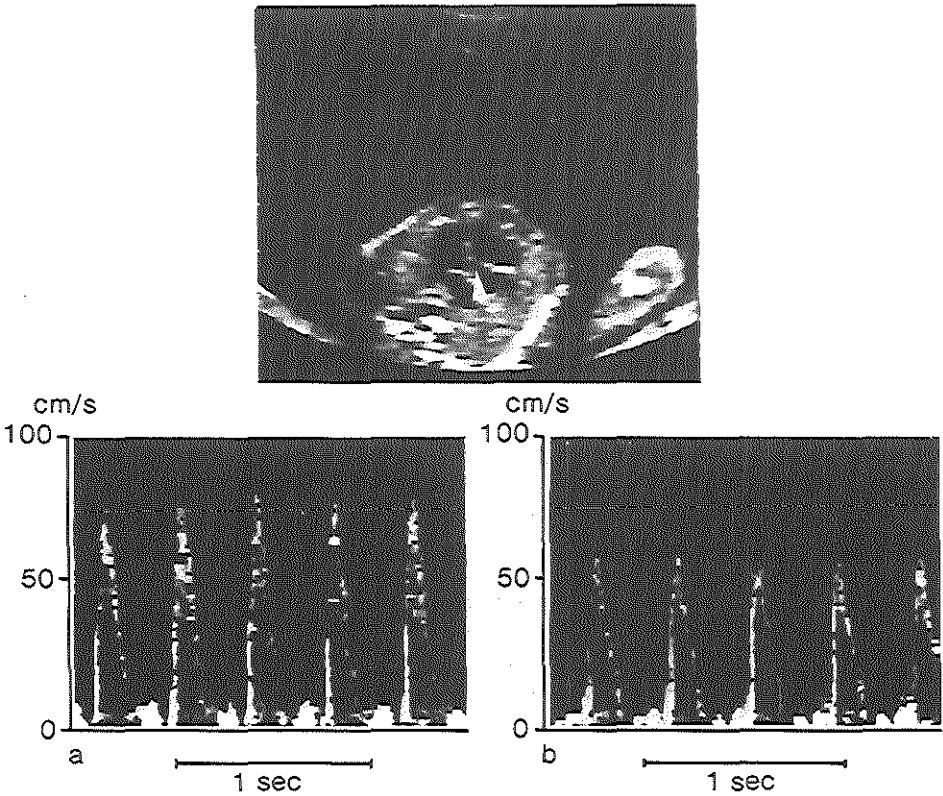
Figure 1. Two-dimensional "five-chamber" view of the human fetal heart with Doppler flow velocity waveforms from the ascending aorta (arrow) during normal pregnancy (a) and IUGR (b).

All Doppler studies were performed with the patient in a semirecumbent position and during periods of fetal apnoea to avoid modulation of the waveforms by fetal breathing movements. Fetal heart rate ranged between 122 and 160 bpm (mean 141 bpm).

Statistical analysis included assessment of the relationship between peak systolic velocities in the cardiac outflow tract and gestational age by repeated measurements analysis of variance, for which the BMDP program 5V (BMDP statistical software manual, University Press of California, Berkely, CA) was used. 5th and 95th percentiles were constructed by taking the estimated regression line ± 1.64 SD. The PSV measurements of the IUGR cases were expressed as SDS. The SDS of a value measured at a certain gestational age is defined as the distance expressed in SD of that value to the mean of the normal reference group at that gestational age.

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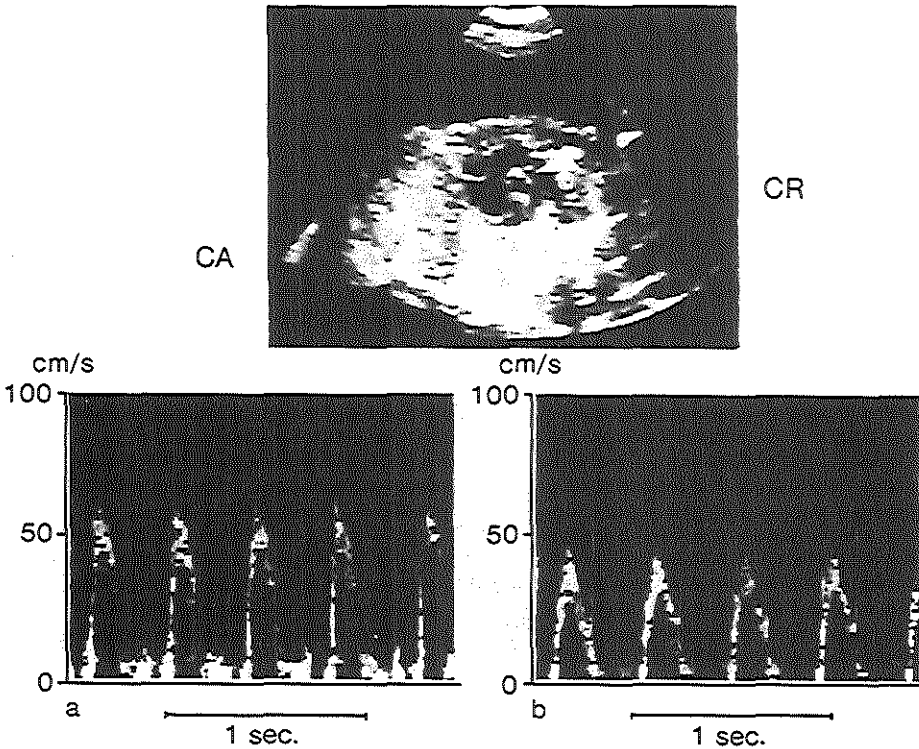
Figure 2. Two-dimensional short axis /pulmonary arterial view of the human fetal heart with Doppler flow velocity waveforms from the pulmonary artery (arrow) during normal pregnancy (a) and IUGR (b). CR, cranial; CA, caudal.

Results

In normal pregnancy (n=46), acceptable flow velocity waveforms were obtained from the pulmonary artery in 147 (80%) and from the ascending aorta in 139 (76%) of the 184 Doppler investigations. The success rate for obtaining acceptable waveforms from both arteries was 66%. PSV in the ascending aorta and the pulmonary artery can be adequately described by a linear function of gestational age, with a constant residual SD around the regression line. The increase in PSV was statistically significant (p<0.001) for both arteries. The mean PSV in the ascending aorta increased from 49.4 cm/s at 19 wk to 79.0 cm/s at 33 wk. During the same gestational period the mean PSV in the pulmonary artery increased from 39.0 cm/s to 63.7 cm/s. The PSV ratio between the ascending aorta and pulmonary artery (PSV AO /PSV PA) remained virtually constant over the entire study period, with mean ratios ranging from 1.25 to 1.29.

Figure 3. Reference curves (5th and 95th percentile) for the PSV AO in normal subjects between 19 and 33 wk of gestation, and data points from 21 IUGR cases. Regression equation for PSV AO $= 9.21 + 2.12 \times$ age; SD $= 5.26$. Closed circles denote intrauterine deaths.

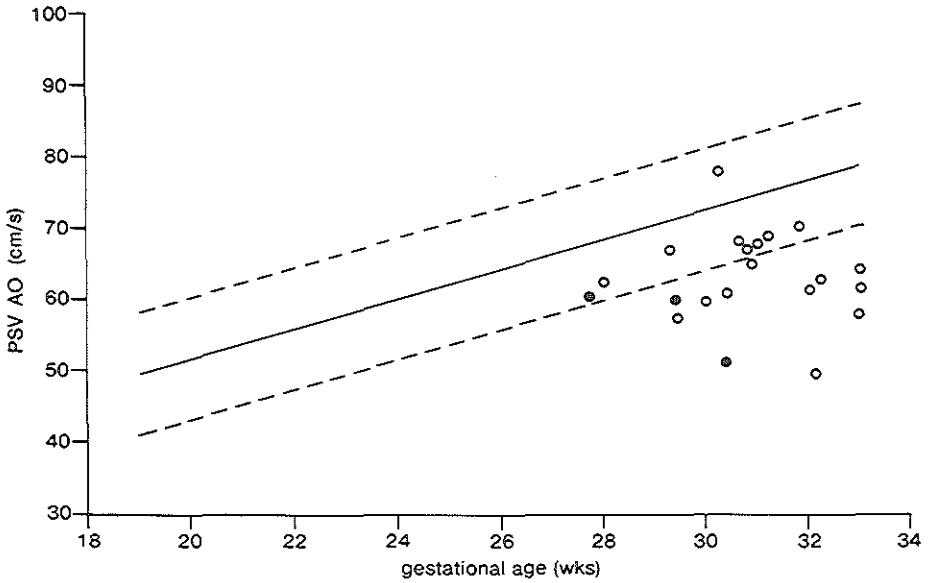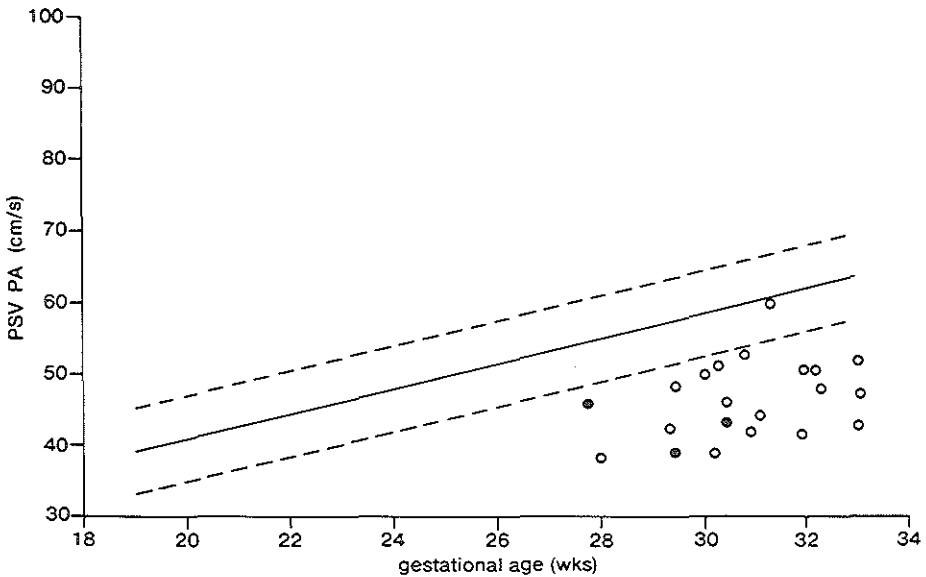Figure 4. Reference curves (5th and 95th percentile) for the PSV PA in normal subjects between 19 and 33 wk of gestation, and data points from 21 IUGR cases. Regression equation for PSV PA $= 5.48 + 1.77 \times$ age; SD $= 3.69$; Closed circles denote intrauterine deaths.

In Figures 3 and 4 the data points for the 21 cases of IUGR are shown with the reference curves. For the PSV in the pulmonary artery, 95% of IUGR cases had decreased ($<$ 5th percentile) values. For the PSV in the ascending aorta, 57% of IUGR cases had reduced ($<$ 5th percentile) measurements. In the umbilical artery, end-diastolic flow velocities were present in eight cases and absent in 13 cases. When comparing PSV values from the cardiac arteries to end-diastolic flow velocity in the umbilical artery, no significant relationship could be established. For the PSV from the ascending aorta the mean SDS (number of standard deviations from the mean) was –2.0 and –2.3 in the presence and absence of end-diastolic flow in the umbilical artery, respectively, whereas for the PSV from the pulmonary artery the corresponding scores were –3.2 and –4.1. For the PSV from the ascending aorta, a statistically significant difference ($p<0.05$, Mann-Whitney test) in mean SDS was established when comparing birth weights below the 2.3 percentile (–3.1) with birth weights between the 2.3 and 5th percentile (–1.7). No such difference could be documented for the PSV from the pulmonary artery, the SDS being –3.9 and –3.6, respectively. No correlation could be established between fetal well-being, as reflected by the Apgar score at 1 min and umbilical arterial pH, and the PSV in either artery. There were three intrauterine deaths that all occurred in utero within 7 days of delivery. Here, the PSV in either artery was not essentially different from those of the surviving IUGR cases.

Discussion

This prospective longitudinal study describes the age-related changes in peak systolic flow velocities across the semilunar valves in the normal human fetus during the second half of gestation. The potential clinical use of flow velocity waveform recordings from the fetal ascending aorta and pulmonary artery is demonstrated by the higher than 75% success rate in obtaining acceptable recordings. Failure to obtain acceptable flow velocity waveforms from these vessels was usually due to excessive fetal movements or maternal obesity. The linear increase of peak systolic flow velocity in both arteries with advancing gestational age is in agreement with other studies (Kenny et al., 1986; Allan et al., 1987; Hata et al., 1987); our own absolute values are similar to those reported by Allan et al. (1987), Huhta et al. (1985) and Reed et al. (1986a), but lower compared with the studies by Hata et al. (1987) and Kenny et al. (1986). This may be due to the fact that angle correction that can give rise to velocity overestimation, was not applied in our study.

Cardiac performance is influenced by heart rate, preload, afterload, and intrinsic properties of both ventricles. From lamb studies it appears that cardiac function is particularly sensitive to changes in afterload (Gilbert, 1982), which is determined by blood pressure and vascular resistance. The gestational age-related rise in normal peak systolic flow velocity in the ascending aorta and pulmonary artery

may be accounted for by increased volume flow through the semilunar valves, raised contractility, or reduced afterload. The noninvasive nature of the human fetal Doppler studies does not allow differentiation between these variables. However, age-related reduction in afterload may occur in the human fetus as a result of the physiologic decrease in placental vascular resistance as expressed by increased end-diastolic flow velocities in the umbilical artery during the second half of gestation (Trudinger et al., 1985). The relationship between peak systolic velocities in the ascending aorta and pulmonary artery appears to be constant during the 3rd trimester of pregnancy with PSV AO /PSV PA ratio values of 1.25 - 1.29, indicating relatively higher peak systolic velocities in the ascending aorta. The latter could be explained by the fact that the afterload to the left ventricle may not only be determined by the umbilical placental and uteroplacental resistance but also by the relatively low resistance at the cerebral level (Wladimiroff et al., 1986; 1988). Alternatively, the aortic valve size has been shown to be smaller than the pulmonary valve size (Allan et al., 1987) and as such may be responsible for the relatively higher peak systolic velocities in the ascending aorta.

The reduced peak systolic velocity values in the fetal ascending aorta and fetal pulmonary artery in IUGR due to impaired placental perfusion is in agreement with a previous cross-sectional study (Groenenberg et al., 1989). Decreased peak systolic velocities could be secondary to reduced volume flow, increased semilunar valve or vessel size, reduced cardiac contractility, or increased afterload. Also, differentiation between these cardiac variables is impossible. However, the absence of tricuspid valve regurgitations makes impaired cardiac contractility less likely. Moreover, in a previous study on IUGR, aortic and pulmonary valve diameters were not essentially different from those observed in normal pregnancies (Reed et al., 1987a). An increase in afterload to both ventricles may be expected on the basis of increased umbilical placental resistance as established by Doppler flow measurements (Wladimiroff et al., 1988). A considerable percentage (43%) of the peak systolic velocities in the ascending aorta were within the normal range. We suggest that this may be determined by the marked reduction in cerebral vascular resistance in IUGR (Wladimiroff et al., 1988), which is in part responsible for the afterload to the left ventricle. This may also explain the relationship between PSV in the ascending aorta and birth weight percentile.

Fetal well-being as expressed by Apgar score and umbilical pH did not correlate with the peak systolic velocity in the fetal ascending aorta and pulmonary artery. We are aware of the fact that particularly the Apgar score is of limited significance in the assessment of fetal outcome.

It can be concluded that there is a linear increase of peak systolic velocity in the ascending aorta and the pulmonary artery during the second half of normal gestation. Higher peak systolic velocities were documented in the ascending aorta relative to the pulmonary artery. In both arteries reduced peak systolic velocities were observed during IUGR, which may reflect increased afterload

to the cardiac ventricles. Whereas a positive correlation was established between the degree of disturbance in fetal growth and peak systolic velocity in the ascending aorta, this was not the case for the pulmonary artery. No correlation existed between peak systolic velocity in both arteries and Apgar score and umbilical cord pH.

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Chapter 5

Fetal cardiac and extra-cardiac flow velocity waveforms relative to perinatal outcome.

Introductory remarks.

A series of reports has appeared on the significance of fetal blood flow velocity waveform recordings in the prediction of adverse fetal outcome. Most studies focus on the umbilical artery and despite different study designs appear to agree on the association between raised pulsatility of the umbilical artery waveform and increased incidence of neonatal hypoxemia and acidemia and neonatal complications necessitating admission to the neonatal intensive care unit (Reuwer et al., 1987; Brar et al., 1989; Chambers et al., 1989; Tyrrell et al., 1989; Lowery et al., 1990; Maulik et al., 1990). Omzigt (1990), in a randomized controlled trial on the clinical value of the availability of umbilical artery waveform recording in antenatal care, observed no differences in birth weight, umbilical acid-base status, admission rate to the neonatal intensive care unit, and the duration and grounds for admission or requirements of ventilatory support. However, in pregnancies considered at risk for fetal distress due to placental circulatory incompetence, a considerable reduction in late fetal deaths was observed in the Doppler group compared to the control group. It was argued that the possible beneficial effect of umbilical artery waveform recording may lie in the selective use of the technique in the management of pregnancies at risk.

The diagnosis and management of IUGR poses a considerable clinical dilemma. Fetal biometry has become effective for defining the group of fetuses at risk for IUGR (Laurin and Persson, 1987a), which prompted Maršál and Persson (1988) to assess the significance of umbilical artery waveform recording as a secondary diagnostic test in screening for intrauterine growth retardation. Compared to pregnancies with normal fetal blood flow, they observed significantly more pregnancy complications and operative deliveries for fetal distress in the presence of abnormal blood flow patterns. It seems, therefore, that umbilical artery waveform recording may have a role to play in the monitoring of high risk pregnancies amidst other diagnostic tools available to the obstetrician.

Whereas most studies focus on the umbilical waveform, virtually no data are available on the possible role of other arterial waveforms in particular from cardiac vessels in identifying the fetus at risk. It has been shown in chapter 4 that in IUGR changes in umbilical artery waveforms are often associated with waveform changes originating from the internal carotid artery and cardiac outflow tract. In this chapter the clinical value of cardiac and extra-cardiac flow velocity waveforms in the prediction of adverse fetal outcome is studied.

In the first part, attention is focused on waveform changes relative to the fetal cardiotocogram serving as a standard for fetal well-being; in the second part waveform data are related to neonatal outcome.

5.1 The monitoring value of flow velocity waveforms in the development of fetal distress; a longitudinal study.

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Summary

In a longitudinal, blinded study design the monitoring value of Doppler velocimetry in predicting fetal distress as determined by daily fetal heart rate recordings was assessed in 42 cases of intrauterine growth retardation. Doppler velocity waveform recordings were obtained at 2-3 day intervals and characterized by the standard deviation score of the pulsatility index in the umbilical artery and internal carotid artery, and the peak systolic and time-average velocity in the ascending aorta, and pulmonary artery. Twenty-seven women did not display fetal distress on the day of entry into the study. During follow up of these women, the pulsatility index in the umbilical artery and internal carotid artery were the most predictive parameters for the development of fetal distress as reflected by the fetal cardiotocogram. The resulting prognostic index was found to have an acceptable discriminative power in the prediction of fetal distress as established in a second group of growth-retarded fetuses.

Key words: Fetal distress, Doppler ultrasonography, Umbilical artery, Internal carotid artery.

Introduction

Less than 40% of pregnancies complicated by intrauterine growth retardation (IUGR) are recognized by maternal signs or symptoms which prompt the clinician to suspect IUGR (Maršál and Persson, 1988). Serial biometric measurements by ultrasound have improved the pick-up rate of IUGR. However, not all those small fetuses are necessarily at risk of becoming asphyctic. Doppler flow velocity

waveform studies in the fetus have provided characteristic changes in various fetal vessels relative to IUGR. In IUGR due to deterioration of placental perfusion, reduced end-diastolic flow velocities in umbilical artery (Trudinger et al., 1985), and descending aorta (Griffin et al., 1984) have been associated with an increase in end-diastolic velocities in intracranial vessels (brain-sparing) (Wladimiroff et al., 1986) and reduced peak systolic flow velocities in the ascending aorta, pulmonary artery and ductus arteriosus (Groenenberg et al., 1989).

Several reports have pointed out the efficacy of blood flow velocity recordings in the umbilical artery in predicting fetal distress, with caesarean section rates, Apgar scores and admission to neonatal intensive care units serving as endpoints (Reuwer et al., 1987). Comparative studies between umbilical artery flow velocity waveform recordings and standard antepartum fetal heart rate testing suggest the former technique to be a valuable adjunct in the antepartum fetal surveillance in high-risk pregnancies (Maršál and Persson, 1988). Despite its limitations, most centres still consider fetal heart rate monitoring as the method of choice in the assessment of fetal distress. No studies are known in which the clinical significance of fetal flow velocity waveforms recording was determined with the fetal heart rate tracing serving as the standard for fetal compromise. The objective of the present study was to assess the significance of serial cardiac and extra-cardiac blood flow velocity waveform recording in the prediction of fetal compromise as determined by the fetal heart rate pattern in IUGR.

Materials and Methods

Forty-two out of 43 women with a singleton pregnancy admitted for IUGR consented to participate in the study. The study protocol was approved by the Hospital Ethics Review Board. IUGR was defined as a fundal growth delay of more than 2 weeks and a deviation of the sonographic fetal upper abdominal circumference to beneath the 10th percentile of the reference curve. Pregnancy duration was determined from the last menstrual period and confirmed by sonographic measurement of the fetal parietal diameter at 14-20 weeks gestation. In 33 women pregnancy was further complicated by pregnancy-induced hypertension. All women were entered into the study within one to 2 days of hospital admission. Gestational age at the entry of the study varied between 26 and 35 weeks of gestation (median 31 weeks). Clinical management consisted of bed rest and treatment of hypertension. The appropriate time of delivery was determined by daily monitoring of fetal heart rate and maternal condition and by gestational age.

Doppler flow velocity waveform recordings were made by an independent observer (I.A.L.G.) on the day of entry into the study (day 1) and subsequently at 2-3 day intervals until delivery. Maximum flow velocity waveforms were recorded at both cardiac and peripheral level, using a combined mechanical sector and pulsed Doppler system (Diasonics CV 400, Diasonics Inc., Mulpikas,

CA). Flow velocity waveforms from the fetal ascending aorta were obtained from the five-chamber view (Groenenberg et al., 1989). Fetal pulmonary artery flow velocity waveforms were recorded from the conventional echocardiographic short axis view (Groenenberg et al., 1989). Doppler sample volumes were placed in the great vessels immediately distal to the semilunar valves. The angle between the Doppler cursor and the assumed direction of flow was always 10 degrees or less. Sample volume length was between 0.2 and 0.4 cm. Peak systolic velocity (PSV, cm/sec) and time-average velocity (AV, cm/sec) were calculated in the ascending aorta (AO) and pulmonary artery (PA). For both parameters a good reproducibility was previously established (Groenenberg et al., 1991). Peripheral arterial Doppler studies were focused on the fetal umbilical artery (UA) and the fetal internal carotid artery (ICA). For both vessels, the pulsatility index (PI) was calculated through dividing the difference between the peak systolic velocity and end-diastolic velocity by the time-average velocity. All flow velocity waveforms were recorded on hard copies for analysis after delivery by a microcomputer (Olivetti M24) linked to a graphics tablet. An average of four consecutive flow velocity waveforms of good quality was used to establish each value.

Fetal cardiotocograms were recorded daily at a median duration of 35 minutes (range 25-60 minutes). After delivery, all recordings were classified by two independent observers (J.W.B. and J.G.S.) according to the Fischer score (Fischer et al., 1976). This score is determined by five variables each being classified as good (2 points), moderate (1 point) or poor (0 points). These variables are: (i) heart rate: 120-160 bpm (good), 100-119 or 161-180 bpm (moderate), <100 or >180 bpm (poor); (ii) heart rate band width: 10-30 bpm (good), 5-10 or >30 bpm (moderate), <5 bpm (poor); (iii) number of zero-crossings per minute of baseline fetal heart rate: >6 (good), 2-6 (moderate), <2 (poor); (iv) heart rate accelerations: sporadic (good), periodic (moderate), absent (poor); (v) heart rate decelerations: absent (good), variable (moderate), late (poor). When the scoring difference between the two observers was 3 points or more, the cardiotocogram was evaluated by a third independent observer, whereby the median value was determined (13 recordings). Assessments were only made during the active sleep state (Nijhuis et al., 1982). Fetal distress was defined as a Fischer score of 6 or less as the longitudinal analysis of data is facilitated by the standard test or outcome to be given as a binary result. A Fischer score of 6 or less associated with cervical priming (n=3) was not regarded as fetal distress, considering that Doppler flow measurements cannot predict fetal compromise when related to an obstetric intervention. The Doppler data of these three patients were only evaluated up to the day of priming.

All Doppler parameters were expressed as standard deviation scores. This score is obtained by taking the difference between the observed value and the mean reference value according to the gestational age and dividing the result by the standard deviation of the reference values (Wladimiroff et al., 1988; Groenenberg et al., 1990). Logistic regression was used to investigate the

relationship between Doppler parameters and the presence of fetal distress on the day of entry into the study (day 1) (Cox, 1970). For women who did not show fetal distress on day 1, Cox-regression with time-dependent variables was used to investigate the relation between the Doppler parameters and the first occurrence of fetal distress during follow up (Cox, 1972). Gestational age served as the time-axis in this analysis. Cumulative percentages of women showing fetal distress during follow up were determined by actuarial methods (Kaplan and Meier, 1958). The log-rank test was used to evaluate differences between groups. P=.05 (two-sided) was considered the limit of statistical significance.

Results

The number of Doppler sessions per subject varied between 1 and 20 (median 8), totalling 247 Doppler sessions and 988 Doppler measurements. The success rate in obtaining technically acceptable Doppler flow velocity waveforms in the umbilical artery, internal carotid artery, pulmonary artery and ascending aorta was 100%, 96%, 94% and 87%, respectively. One woman dropped out two weeks after hospital admission, due to referral to another hospital. Doppler and heart rate data selected during these weeks were included in the analysis. Fetal birth weight varied between p<2.3 and p25 (median p5) according to Kloosterman's Tables corrected for maternal parity and fetal sex (Kloosterman, 1970). Caesarean section was performed in 36 women, vaginal delivery took place in the remaining 6 women (including one intrauterine death). Umbilical artery pH after delivery ranged between 6.82 and 7.33 (median 7.20).

Fifteen out of 42 women displayed fetal distress on day 1 (day of entry into the study). The presence of fetal distress on day 1 correlated significantly with gestational age: women with fetal distress were of a significantly (Mann-Whitney's test: p=.03) lower gestational age than those without fetal distress (mean 29.8 weeks, SD 1.8 versus mean 31.3 weeks, SD 2.5). Table 1 presents data on the various Doppler parameters, expressed as standard deviation score according to whether or not fetal distress was present on day 1. When taking into account gestational age, PIUA and PSVAO scores separately showed a significant correlation with the occurrence of fetal distress on day 1. Simultaneous evaluation of these flow parameters, however, demonstrated that only the PIUA score remained significantly correlated with fetal distress (Table 2).

Longitudinal data from the remaining 27 women (788 Doppler measurements) in which fetal distress was absent on day 1, were used to establish the monitoring value of Doppler recordings for the development of fetal distress during the course of pregnancy. Fourteen women developed fetal distress, 13 women did not. All 14 women developing fetal distress were delivered by caesarean section, whereby the time delay between the occurrence of fetal distress and delivery ranged between 0 and 15 days (71% within 2 days of delivery). Five out of 13 women who did not develop fetal distress were delivered vaginally. In the

Table 1. Mean scores (± SD) of Doppler parameters in the presence or absence of fetal distress on the day of entry into the study. PIUA, PIICA = pulsatility index in umbilical artery and internal carotid artery. PSVAO, AVAO = peak systolic and time-average velocity in ascending aorta. PSVPA, AVPA = peak systolic and time-average velocity in pulmonary artery.

| Doppler parameter | fetal distress | | | | | | |
| | present | | | absent | | | |
	mean	sd	n	mean	sd	n	p(*)
PIUA	+12.0	11.0	15	+3.7	4.0	27	.001
PIICA	-2.9	1.1	15	-2.4	1.5	26	.09
PSVAO	-1.6	0.9	14	-0.9	1.4	22	.04
AVAO	-1.4	1.0	14	-0.8	1.1	22	.08
PSVPA	-2.8	1.8	14	-2.2	1.5	23	.16
AVPA	-2.2	1.7	14	-1.8	1.3	23	.21

(*) Significance, adjusted for gestational age (logistic regression). Total number of patients not always 42 due to different success rates for various vessels.

Table 2. Multivariate analysis of gestational age, PIUA scores and PSVAO scores on the day of entry into the study. Data given are odds-ratios for fetal distress (odds-ratio = 1 indicates no relation).

variable	odds-ratio	p value	confidence limits (90%)
gestational age	1.3[a]	.10	1.0-1.8
PIUA	1.2[b]	.007	1.0-1.4
PSVAO	1.3[c]	.47	0.7-2.6

relative to (a) 1 week later in gestation, (b) 1 standard deviation score lower, (c) 1 standard deviation score higher.

remaining eight women caesarean section was performed because of partial abruptio placentae (n=2), severe preeclampsia (n=4) or gestational age of 36 weeks or more in the presence of non-optimal cardiotocograms (n=2). Cox-regression revealed that the PIUA, PIICA, PSVAO and AVAO scores were significantly correlated with the incidence of fetal distress. However, when each parameter was evaluated separately from simultaneous assessment of these variables, it appeared that the correlation only remained significant for the PIUA and PIICA scores (Table 3). The multivariate assessment of the PIUA and PIICA scores resulted in a prognostic index for the development of fetal distress during follow up: 0.43 × PIUA score – 0.96 × PIICA score. Figure 1 depicts the values of this index for the 27 women during follow up. Data points for the 14 women

Table 3. Multivariate analysis of PIUA, PIICA, PSVAO and AVAO scores with respect to the incidence of fetal distress.

variable	relative rate of fetal distress	p value	confidence limits (90%)
PIUA	1.4[a] (1.5)	.05 (.01)	1.1- 1.8
PIICA	3.1[b] (2.6)	.10 (.05)	1.0- 9.8
PSVAO	0.7[c]	.66	0.2- 2.4
AVAO	3.6[d]	.22	0.7-19.9

relative to (a) 1 standard deviation score lower, (b,c and d) 1 standard deviation score higher. Data between parenthesis apply to simultaneous assessment of PIUA and PIICA only.

developing fetal distress are interconnected, with the last data point representing the Doppler measurement obtained within 24 hours prior to the occurrence of fetal distress. As can be seen, the prognostic index values of women developing fetal distress tend to be higher than those who did not. The prognostic index appears to increase with advancing gestational age. By fitting a least-squares regression line (I) through the data points not associated with fetal distress, the
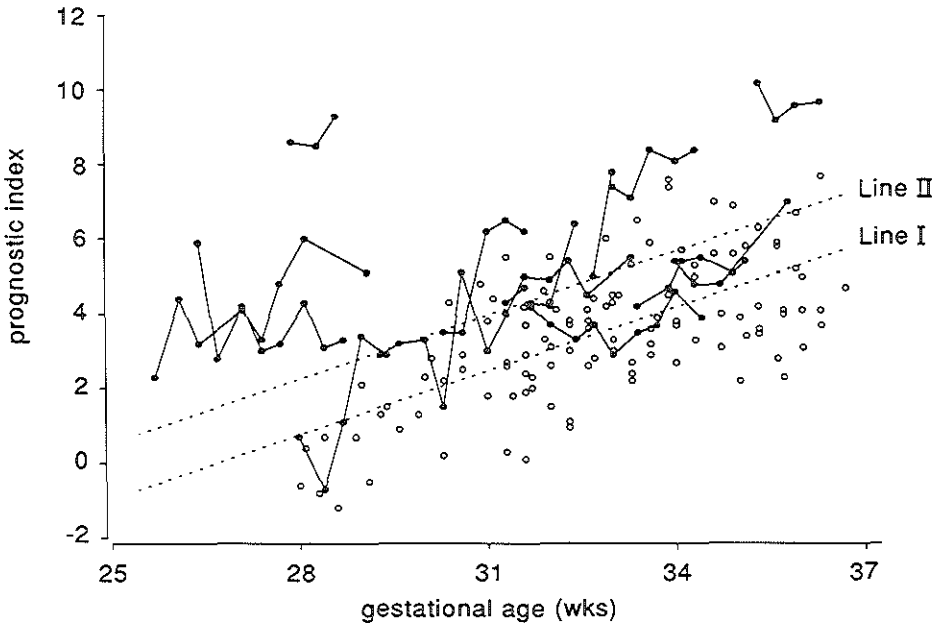

Figure 1. Prognostic index values against gestational age. Data points of women developing fetal distress are interconnected (n=14), data points of women who never developed fetal distress (n=13) are given as individual data points. Line I: least-square regression line through prognostic index values of women without fetal distress. Line II: cut-off level, 1 SD above line I.

rising trend of the prognostic index was characterized. To evaluate the prognostic value of the index, a cut-off level (II) was drawn 1 SD above and parallel to the regression line. In 18 out of 27 women, index values were situated above this cut-off level at least once during follow up. For this group of women, the actuarial cumulative percentage of women who developed fetal distress was determined according to the number of days past the day on which a particular prognostic index value was first situated above the cut-off level (Figure 2). The percentage of women who had developed fetal distress amounted to 46% within 1 week and 76% within 4 weeks. In the 13 women who had not developed fetal distress (111 successful Doppler measurements), 14 prognostic index values (13%) were situated above the cut-off level. In the remaining 14 women, 76 successful Doppler measurements were obtained prior to the development of fetal distress. Forty-four prognostic index values (58%) were situated above the cut-off level. If only the last three prognostic index values prior to the development of fetal distress were taken into account, then the percentage rose to 71%. Women (n=27) were also grouped according to whether the prognostic index value was situated above the cut-off level (Figure 1) on day 1 or not. In the former group (n=10), 43% of women had developed fetal distress within one week, whereas in the latter group (n=17), this percentage was only 7%. This difference, however, is not statistically significant (p=.15).
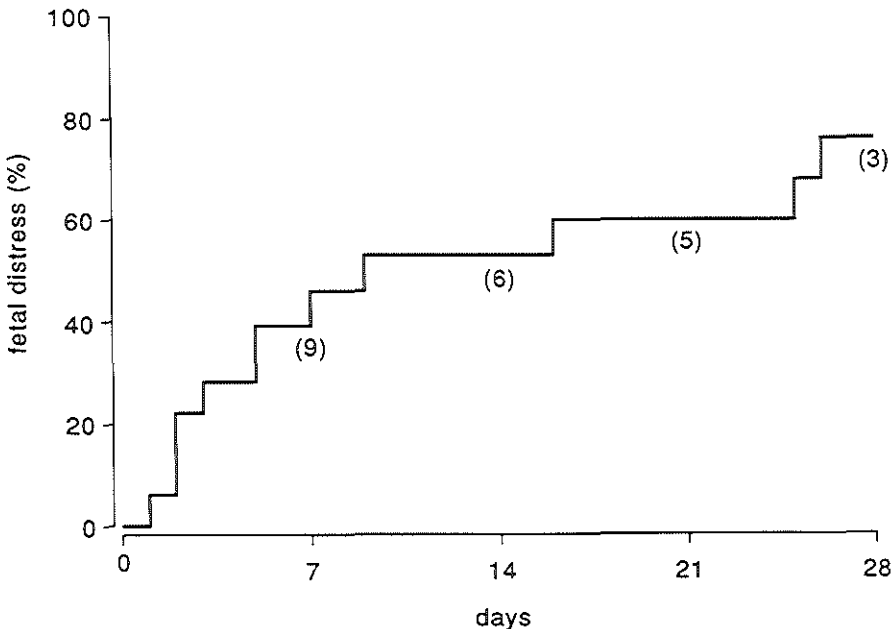

Figure 2. Cumulative percentages of women developing fetal distress. The horizontal axis represents the number of days following the day that the prognostic index rose above the cut-off level. Numbers between parentheses denote number of women still at risk for fetal distress.

To validate the prognostic index, Doppler data of 25 IUGR cases from a previous cross-sectional study (Groenenberg et al., 1989) were reviewed. Data from 18 women, who were not displaying fetal distress on the day at which the fetal Doppler recording was obtained, were available for this evaluation. Fifteen out of 18 women subsequently developed fetal distress, all but one of which displayed a prognostic index value above the cut-off level depicted in Figure 1. In the remaining 3 women, the prognostic index was situated below this level.

Discussion

Previous studies in high risk pregnancies have related Doppler flow velocity waveforms to neonatal outcome, thereby comparing Doppler data with that of fetal heart rate monitoring (Devoe et al., 1990). It has been suggested that fetal compromise is more efficiently recognized by fetal flow velocity waveform recording (Hackett et al., 1987), whereas others (Lowery et al., 1990) consider these Doppler recordings to have a significant complementary value to traditional antepartum testing.

Unlike these reports, the present study describes the use of Doppler flow measurements as a monitoring tool in predicting prenatal distress as determined by the fetal cardiotocogram. Our finding of Fischer scores being significantly related to gestational age on the day of entry into the study, is likely to be a consequence of patient selection, since particularly cases of early developing IUGR are referred from district hospitals to academic centres for close fetal monitoring. Taking into account the gestational age, both the PIUA scores and PSVAO scores appeared to have a predictive value regarding the development of fetal distress on the day of entry into the study. However, no additional information is provided by the PSVAO score when the PIUA score is known. The risk of fetal distress went up sharply with increasing PIUA.

Of particular interest is the course of pregnancy during hospitalization. Several studies have shown that changes in Doppler parameters may precede deterioration in fetal heart rate patterns (Bekedam et al., 1990). This is the first study to demonstrate that PIUA, PIICA, PSVAO and AVAO scores are related to the development of fetal distress as reflected by the fetal cardiotocogram. Also here, the cardiac parameters do not contribute to the assessment of fetal condition when the combined PIUA and PIICA scores are known. The derived prognostic index, therefore, only includes the PIUA and PIICA scores. The inclusion of the PIICA emphasizes the pathophysiological importance of a reduced cerebral vascular resistance (so-called brain-sparing) in intrauterine growth retardation. Validation of the derived prognostic index in a second group of growth-retarded fetuses confirmed its predictive value. With the introduction of Doppler flow measurements, an increasing number of clinicians appears to be in favour of delivering the infant at an earlier stage in pregnancy instead of waiting until

the fetal cardiotocogram becomes abnormal (Hackett et al., 1987). In this context the close time-relationship observed in the present study between the development of abnormal Doppler flow velocity waveforms resulting in a raised prognostic index value and the development of fetal distress is of particular importance. Nearly 50% of women with a raised prognostic index developed fetal distress within a period of one week. The majority of women who did develop fetal distress were delivered within 24 hours. However, two were delivered 8 days, and one even 15 days later. The time delay in the last three cases was determined by severe prematurity (less than 28 weeks) at the time of fetal distress. The percentage of prognostic index values which were situated below the cut-off level (42%) in women who developed fetal distress after all and the percentage of prognostic index values which were situated above the cut-off level (13%) in women who did not develop fetal distress, demonstrates the satisfactory discriminative power of this index in IUGR. This is further emphasized by the low percentage (29%) of prognostic index values below the cut-off level when only the last three index values prior to fetal distress are considered. Further prospective studies are needed to obtain guidelines for optimal incorporation of Doppler measurements in obstetric management.

It can be concluded that the PI in the umbilical artery and internal carotid artery are predictive for the development of fetal distress as reflected by the fetal cardiotocogram.

5.2 Relationship between fetal cardiac and extra-cardiac Doppler flow velocity waveforms and neonatal outcome in intrauterine growth retardation.

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Summary

In a total of 42 consecutive pregnancies with intrauterine growth retardation (IUGR), Doppler velocimetry was related to neonatal outcome as determined by: Apgar score at 1 minute, umbilical artery acid-base status and pO_2, number of nucleated red blood cells (NRBC), duration of ventilatory support, and

sonographic appearance of cerebral leukomalacia. Doppler flow velocity waveforms were obtained from the ascending aorta (AO), pulmonary artery (PA), internal carotid artery (ICA), and umbilical artery (UA) at 2-3 day intervals until delivery. At cardiac level the peak systolic velocity (PSV) and time-average velocity (AV), and at peripheral level the pulsatility index (PI) was determined. As all Doppler parameters were significantly related to gestational age at birth, gestational age was taken into account in the analysis. There was no relationship between Apgar score, acid-base status and Doppler parameters. Low AVAO was related to a low umbilical artery pO_2. Significant correlations were established between PSVPA, AVPA and PIUA, and the duration of neonatal ventilatory support. Infants who died within 22 days after admission to the neonatal intensive care unit (n=7) displayed a significantly higher PIUA than those who remained alive. The PIUA was also related to the absolute and relative number of NRBCs. No relationship existed between the Doppler parameters and degree of leukomalacia. The present study demonstrates that from all Doppler parameters, the PIUA is most clearly related to neonatal outcome in IUGR.

key words: Intrauterine growth retardation, Fetal cardiac outflow tract, Doppler ultrasonography, Neonatal outcome.

Abbreviations

AVAO	average velocity in ascending aorta
AVPA	average velocity in pulmonary artery
IUGR	intrauterine growth retardation
NICU	neonatal intensive care unit
NRBC	nucleated red blood cell
PIICA	pulsatility index in internal carotid artery
PIUA	pulsatility index in umbilical artery
PSVAO	peak systolic velocity in ascending aorta
PSVPA	peak systolic velocity in pulmonary artery
PVH	periventricular haemorrhage
PVL	periventricular leukomalacia
WBC	white blood cell

Introduction

Doppler flow velocity waveforms from the umbilical artery and fetal descending aorta have been related to adverse outcome, as determined by Apgar scores, umbilical cord acid-base status and admission rate to the neonatal intensive care unit (Laurin et al., 1987b; Rochelson et al., 1987; Brar et al., 1989; Tyrrell et al., 1989; Maulik et al., 1990). Perinatal asphyxia is likely to predispose infants to cerebral injury such as periventricular haemorrhage (PVH) and periventricular

leukomalacia (PVL) (Weindling et al., 1985). Increased nucleated red blood cell (NRBC) counts have also been related to asphyxia. A cordocentesis study by Soothill et al. (1987) suggested a relationship between chronic hypoxia and elevated NRBC counts in intrauterine growth retardation (IUGR). A similar relationship between elevated NRBC counts and growth retardation was established in the neonate (Philip and Tito, 1989).

Cardiac flow velocity waveforms have demonstrated reduced peak systolic velocities at outflow tract level in IUGR (Groenenberg et al., 1989). No information is available on the significance of these cardiac flow velocities in the prediction of neonatal outcome.

In the present study, therefore, attention was focused on the relationship between both fetal cardiac and peripheral arterial blood flow velocity waveforms and neonatal outcome as determined by : i) Apgar score at 1 minute, umbilical artery acid-base status and oxygen tension, ii) admission rate to the neonatal intensive care unit and requirement of positive pressure ventilatory support, iii) nucleated red blood cell counts and, iv) sonographic appearance and degree of periventricular leucomalacia in the neonatal period.

Materials and Methods

Out of 43 consecutive women with IUGR, 42 consented to participate the study. IUGR was defined as a fundal growth delay of more than two weeks and a deviation of the sonographic fetal upper abdominal circumference to beneath the 10th percentile of the reference curve (Campbell, 1976). Pregnancy duration was determined from the last menstrual period and confirmed by ultrasonic measurements of the biparietal diameter at 14 - 20 weeks gestation. In 33 women pregnancy was further complicated by pregnancy-induced hypertension. Gestational age at the entry into the study ranged from 26 to 35 weeks of gestation (median, 31). The study protocol was approved by the Hospital Ethics Committee.

Doppler flow measurements were performed by one observer (I.A.L.G) at 2-3 day intervals until delivery. The last Doppler measurement before delivery was related to neonatal outcome. Doppler data were blinded to the obstetric staff. A combined mechanical sector and pulsed/continuous Doppler system (Diasonics CV 400, Diasonics Inc., Mulpikas, CA) with a carrier frequency of 3.5 and 3.0 MHz was used. The sector scanner operates at power outputs of less than 100 mW/cm^2 spatial peak-temporal average in both imaging and Doppler modes by manufacturer's specifications. In each instance, the correct position of the pulsed Doppler gate was ensured by two-dimensional ultrasound both before and after each Doppler tracing was obtained. Maximum flow velocity waveforms were recorded at both cardiac and peripheral level. At cardiac level, Doppler recordings were produced from the fetal ascending aorta (AO) and pulmonary artery (PA). Flow velocity waveforms from the fetal ascending aorta

were obtained from the five-chamber view (Kenny et al., 1986). Fetal pulmonary artery flow velocity waveforms were recorded from the conventional echocardiographic short axis view (Kenny et al., 1986). The Doppler sample volume was placed in the great vessels immediately distal to the semilunar valves. The angle between the Doppler cursor and the assumed direction of flow was always 10 degrees or less. Sample volume length was between 0.2 and 0.4 cm. Peak systolic velocity (PSV, cm /sec), and time-average velocity (AV, cm /sec) were calculated.

Peripheral arterial Doppler studies were focused on the fetal umbilical artery (UA) (McCallum et al., 1978) and the fetal internal carotid artery (ICA) (Wladimiroff et al., 1986). Both for the umbilical artery and internal carotid artery the pulsatility index (PI) was calculated. The PI is derived by dividing the difference between the peak systolic and end-diastolic velocity by the mean velocity over the entire cardiac cycle (Gosling and King, 1975).

All Doppler studies at cardiac and peripheral level were performed with the patient in the semirecumbent position and during periods of fetal apnoea, because high amplitude fetal breathing movements modulate blood flow velocity waveforms. All flow velocity waveforms were recorded on hard copies. A microcomputer (Olivetti M24) linked to a graphics tablet was used for analysis of the Doppler recordings. An average of four consecutive flow velocity waveforms with the highest velocity and of similar appearance was used to establish each value.

Neonatal outcome was expressed by Apgar score at 1 minute, umbilical artery pH, Base Excess (BE, mEq /l), and oxygen tension (pO_2, KPasc).

Thirty-three infants were admitted to the neonatal intensive care unit (NICU) of the Sophia Children's Hospital and 5 infants were referred to the NICU of a district hospital.

A nucleated red blood cell count (NRBC) was performed in 26 infants admitted to the NICU of the Sophia Children's Hospital. Total white blood cell count (WBC) was determined within 12 hours after birth and the number of NRBCs was calculated from examination of the blood smear for the differential WBC count. The WBC count was then corrected for the NRBC count. NRBCs were determined as NRBCs per 100 WBCs and as absolute NRBC counts by multiplying the (corrected) WBC count by the percentage of NRBCs.

Cerebral scans were performed in 28 infants admitted to the NICU of the Sophia Children's Hospital at 2/3, 6/7 and 10/11 days after delivery. These were performed through the anterior fontanelle using a Diasonics scanner (ADA 400), with a 7.5 MHz transducer by one observer (W.B). Abnormal ultrasound findings were classified into three groups: PVL stage 0; flaring alone, PVL stage I; flaring without visible cystic changes, but followed by ventricular dilatation, PVL stage II; cystic periventricular leukomalacia characterized by intense bilateral flaring of the periventricular areas, followed by polycystic degeneration (Baerts et al., 1990). For further analysis, the infants were judged according to their severest degree of leukomalacia as documented during the first 11 days of

postnatal life.

Multiple regression analysis was used to simultaneously investigate the relationship of the Doppler measurements and gestational age with pregnancy outcome. The Mann-Whitney U test was used for comparing the Doppler data with the results of the brain scans, and postnatal deaths. P=.05 (two-sided) was considered the limit of statistical significance.

Results

Birth weight (median, 1055g) varied between p<2.3 and p25 (median, p5) according to Kloosterman's Tables corrected for maternal parity and fetal sex (Table 1) (Kloosterman, 1970). There was one intrauterine death. Five women were delivered vaginally. Thirty-six woman were delivered by caesarean section, 28 of which because of fetal distress as determined by the fetal cardiotocogram. In the remaining eight women, caesarean section was performed because of partial abruptio placentae (n=2), severe preeclampsia (n=4) or gestational age of 36 weeks or more in the presence of suboptimal cardiotocograms (n=2). The time delay between the last Doppler measurement and delivery varied between 0 and 6 days (median, 1). One woman was excluded from the study because of a time delay of 20 days, leaving 40 patients for further analysis.

The time delay between the entry of the study and delivery varied between 1 day and 7 weeks (median 2.5 wk). The success rate for obtaining acceptable blood flow velocity waveforms (last measurement) in the umbilical artery, internal carotid artery, ascending aorta and pulmonary artery was 100%, 95%, 93%, and 88%, respectively. PIUA and PIICA were situated outside the reference curves ($\pm$ 2 SD) (Wladimiroff et al., 1988; Groenenberg et al., 1990) in 78% and 87%, respectively. For the PSVAO and PSVPA the percentages were 63 and 84. No reference charts are available for the AVAO and AVPA. All Doppler parameters significantly correlated with gestational age at birth. A negative

Table 1. Data on neonatal outcome.

	median	range	n
gestational age at birth (wks)	32	28 - 37	40
birth weight (g)	1055	395 - 2030	40
Apgar at 1 min	6	1 - 10	40
pH	7.20	6.82 - 7.33	40
BE	−7.0	-0.9 - −24.2	39
pO$_2$ (kPasc)	1.37	0.48 - 2.53	24

correlation was established for the PIUA, and PIICA (r=−.32, and r=−.40, respectively), whereas a positive correlation was established for the PSVAO, AVAO, PSVPA, and AVPA (r=+.49, r=+.36, r=+.56, and r=+.47, respectively).

Table 1 presents data on Apgar scores at 1 minute and postnatal umbilical artery pH, BE, and pO_2. No correlation could be established between Apgar score at 1 minute and the Doppler parameters. No correlation existed between the Doppler flow velocity parameters from the internal carotid artery, and pulmonary artery, and postnatal umbilical artery pH, BE and pO_2. PIUA was significantly related to pH and BE. However, this relationship disappeared when taking into account gestational age. PSVAO and AVAO were significantly correlated with pO_2 (r=+.44, p=.04; r=+.57, p=.007, respectively), when gestational age was taken into account, this relationship only remained significant for AVAO.

Eighteen neonates required positive pressure ventilation. Duration of ventilation varied between 1 and 38 days (median, 8 days). All flow parameters except for the PIICA correlated significantly with the duration of ventilation. After multiple regression taking into account gestational age, this correlation only remained significant for the PSVPA (r=−.46, p=.006), AVPA (r=−.54, p=.001), and PIUA (r=+.42, p=.007).

There were 7 postnatal deaths; one infant died immediately after birth, and 6 infants died within 22 days after admission to the NICU. These neonates displayed a significantly higher PIUA (mean 4,07, SD 1.58) compared to those who remained alive (2.05, SD 1.39; p<.001). After multiple regression, taking into account gestational age, this correlation remained significant (p=0.01).

NRBC/100 WBC varied between 11.5 and 3350 (median, 125), absolute NRBC count ranged between 0.6×10^9 and 164×10^9/L (median, 7.7×10^9). Because of the skewed distributions, the logarithm of both NRBC counts and absolute number of NRBCs was used in the analysis. Both the NRBC/100 WBC and absolute NRBC count were significantly correlated with PIUA (r=+.64, p<.001, and r=+.61, p=<.001, respectively). Taking into account gestational age, the correlation remained significant (p=.001).

Brain scans were performed in 28 infants, 19 of which showed no abnormalities. A subdural haemorrhage was seen in one infant. PVL stage 0, I and II were seen in 2, 2 and 4 infants, respectively. Doppler flow velocity waveforms from infants with PVL stage I and II were not significantly different from those with PVL stage 0 or from those with normal scans.

Discussion

The majority of reports agree upon a possible role of Doppler flow velocity waveforms in the surveillance of high-risk pregnancies (Laurin et al., 1987b; Rochelson et al., 1987; Brar et al., 1989; Tyrrell et al., 1989; Maulik et al.,

1990). These studies reveal relationships with pregnancy outcome in various obstetric populations. However, as the majority of clinical endpoints and Doppler parameters are age related, one may question as to whether Doppler flow velocity waveforms provide additional information about adverse perinatal outcome. Indeed, in the present study, the greater number of correlations of Doppler parameters with neonatal outcome disappear when correcting for gestational age.

Flow velocity waveforms in the fetal descending aorta and umbilical artery have been related to fetal acid-base status and oxygen tension prenatally and at delivery (Laurin et al., 1987b; McCowan et al., 1987; Ferrazzi et al., 1988; Nicolaides et al., 1988; Wladimiroff et al., 1988; Brar et al., 1989; Tyrrell et al., 1989). In pregnancy populations suspected of IUGR, contradictory results have been reported: Wladimiroff et al. (1988) and Ferrazzi et al. (1988) found a correlation between pH at delivery and PI in the umbilical artery, whereas McCowan et al. (1987) did not. This may be explained by differences in study populations, effect of the process of birth on acid-base status or the limited number of patients. No significant relationship has been reported between the PI in the fetal thoracic descending aorta and pH (Laurin et al., 1987b). Our data indicate that the correlation between PIUA and pH is mainly determined by gestational age. Similar results have been reported by Bekedam et al. (1990) who compared IUGR fetuses with end-diastolic velocities in the umbilical artery with those without end-diastolic velocities. After matching for gestational age and birth weight the difference between the two groups in pH and pO_2 disappeared. A relationship between flow velocity waveforms in the umbilical artery (Nicolaides et al., 1988) and in thoracic descending aorta (Soothill et al., 1986) and fetal pO_2 and pH has been established in cordocentesis studies. Our observation of a correlation between the time-average velocity in the fetal ascending aorta and pO_2 at delivery is in agreement with the findings made at cordocentesis. It has been suggested (Soothill et al., 1986) that these correlations may be related to increased placental vascular impedance or redistribution of blood flow during hypoxemia. In IUGR, reduced peak systolic velocities in the ascending aorta and pulmonary artery have been associated with raised vascular resistance at fetal trunk and placental level, whereby the afterload to the left ventricle is also determined by cerebral vascular resistance (Groenenberg et al., 1989). PI values in the internal carotid artery suggest a reduced vascular resistance at cerebral level in all but one of the fetuses. The positive correlation between time-average velocities in the ascending aorta and umbilical artery pO_2 may, therefore, be explained by differences in placental vascular impedance. Since Doppler data from the umbilical artery and pulmonary artery were not related to umbilical artery pO_2, the meaning of this relationship is not clearly understood. The lack of any correlation between cardiac and extra-cardiac flow velocity waveforms and Apgar score may be determined by the crudeness of the scoring system.

Of interest is that low time-average and peak-systolic velocities in the

pulmonary artery, and a high PI in the umbilical artery are associated with an increased duration of ventilatory support in the 18 neonates in the NICU. The PI in the umbilical artery reflects downstream impedance, and therefore umbilical placental resistance. As mentioned earlier, a similar relationship has been assumed for peak systolic velocities in the pulmonary artery, whereby reduced velocities are associated with increased vascular resistance. This suggests that besides gestational age, impaired placental function may be a determinant of requirement of positive pressure ventilation.

The PIUA seems to be clearly related to neonatal outcome, which is also demonstrated by the positive correlation between PIUA and neonatal mortality. Hackett et al. (1987) and Bekedam et al. (1990) found an increased mortality in IUGR fetuses with absent end-diastolic velocities compared to those with end-diastolic velocities in the umbilical artery. In contrast to our findings, no significant difference in mortality was found when selecting a subgroup matched for gestational age and birth weight (Bekedam et al., 1990). In this respect one may hypothesize about a possible reduction in postnatal deaths if timing of delivery would have been based on umbilical artery Doppler surveillance. In a randomized trial, Omzigt (1990) found a reduction in late fetal deaths in the Doppler group compared to the control group. However, no differences in neonatal mortality and morbidity could be demonstrated.

A perinatal increase in nucleated red blood cell counts (NRBC counts) has been reported in growth retardation (Soothill et al., 1987; Philip and Tito, 1989). It has been suggested that increased NRBC counts may be related to chronic perinatal hypoxemia. This is in support of the positive correlation between the number of NRBCs per 100 WBC and the absolute number of NRBCs, and PIUA, reflecting raised placental vascular resistance and therefore impaired placental perfusion.

Cerebral injury may be one of the neonatal complications in IUGR. Extensive cystic leukomalacia (PVL) is associated with cerebral palsy later in infancy (Weindling et al., 1985). Cystic leukomalacia is often preceded by so-called flaring, which are echodense periventricular areas. The prognosis of transient flaring or flaring not followed by the development of periventricular cysts (PVL stage 0) appears to be relatively good (Levene, 1990). Therefore, in the present study infants with PVL stage 0 and normal scans were compared to those with PVL stage I or II. Scans were only performed in the first two weeks postnatally, as changes related to prenatal hypoxemia appear during this period (personal communication W.B.). Only 6 out of 28 infants undergoing serial brain scans displayed leukomalacia stage I or II. This may explain the lack of any correlation between the Doppler parameters and sonographically determined neonatal leukomalacia.

Although some of the obtained relationships only apply to neonates requiring intensive care, it can be concluded that from all Doppler parameters, the PIUA is most clearly related to neonatal outcome in IUGR.

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Chapter 6

General conclusions

In this thesis Doppler flow velocity waveforms from different levels of the circulatory system in the growth-retarded fetus were studied.

At cerebral level flow velocity waveforms from the internal carotid artery, middle cerebral artery, anterior cerebral artery, and posterior cerebral artery show a significant increase in end-diastolic velocities as compared to normal pregnancy. It is suggested that these raised end-diastolic velocities reflect reduced cerebral vascular resistance. This is in accordance with the results of animal experimental studies which demonstrate a redistribution of blood flow favouring the brain, heart and adrenal glands.

At peripheral level reduced end-diastolic velocities are observed in the descending thoracic aorta, umbilical artery, and maternal uteroplacental artery, suggesting an increase in uteroplacental and umbilical placental resistance in intrauterine growth retardation (IUGR).

At cardiac level a high reproducibility of flow velocity waveform recording and waveform analysis is achieved for the peak systolic velocity, average velocity, and flow velocity integral in the ductus arteriosus, ascending aorta, and pulmonary artery. Whereas a moderate reproducibility is achieved for the acceleration time in the ascending aorta and pulmonary artery, the variation in acceleration velocity for all cardiac vessels studied, and the variation in acceleration time in the ductus arteriosus is unacceptably large.

In normal pregnancy peak systolic velocity in the ascending aorta and pulmonary artery show a linear increase with advancing gestational age. In IUGR, a significant reduction in peak systolic velocity in the ductus arteriosus, ascending aorta, and pulmonary artery is observed. This may be explained by reduced volume flow, increased valve or vessel size, or raised afterload. The magnitude of the reduction in peak systolic velocity in the pulmonary artery was larger than that in the ascending aorta. This may be explained by differences in afterload: the afterload to the right ventricle is mainly determined by the resistance at fetal trunk and placenta, whereas the afterload to the left ventricle is also determined by cerebral vascular resistance, which is decreased in IUGR. This assumption is further supported by the finding that the peak systolic velocity in the pulmonary artery is related to the degree of placental infarction in IUGR.

Peak systolic velocities in the ascending aorta and pulmonary artery are not related to the presence or absence of end-diastolic velocities in the umbilical artery.

Whereas flow velocity waveforms from the ascending aorta and pulmonary artery are not predictive for the development of fetal distress as determined

by a Fischer score of 6 or less from the fetal cardiotocogram, flow velocity waveforms from the umbilical artery and internal carotid artery characterized by the pulsatility index are predictive for the development of fetal distress during follow up. Further prospective, blinded studies are needed to evaluate the clinical value of flow velocity waveforms from the umbilical artery and internal carotid artery for the development of fetal distress.

Compared with flow velocity waveforms from the ascending aorta, pulmonary artery and internal carotid artery, flow velocity waveforms from the umbilical artery display the closest relationship with neonatal outcome. Taking into account gestational age, there is a significant relationship between the umbilical artery pulsatility index and neonatal mortality, duration of ventilatory support in the neonatal intensive care unit and number of neonatal nucleated red blood cells. However, as gestational age is an important determinant of neonatal outcome, it remains to be seen as to whether umbilical artery Doppler surveillance will improve neonatal outcome.

Summary

Chapter 1

Intrauterine growth retardation (IUGR) is a major obstetric problem as it contributes to a significant extent to perinatal morbidity and mortality. Despite the availability of several diagnostic tools for diagnosis and surveillance, antenatal diagnosis of IUGR is difficult and inaccurate. The use of Doppler ultrasound has emphasized the hemodynamic redistribution occurring in IUGR as has been demonstrated in animal experimental work. The objective of the present study was to document the changes in Doppler flow velocity waveforms at fetal cardiac and peripheral level and to relate these to changes in fetal heart rate patterns, fetal outcome and neonatal outcome. Furthermore, the reproducibility of fetal cardiac blood flow velocity waveforms is assessed.

Chapter 2

This chapter deals with methodological and animal experimental aspects of fetal hemodynamics relative to growth retardation. Problems encountered when performing Doppler flow measurements are emphasized, both in case of volume flow measurements and qualitative approaches. Furthermore, (patho)physiological mechanisms underlying changes in Doppler flow velocity waveforms are discussed. In the second part of this chapter results of animal experimental work is presented. Hemodynamic responses of the fetal lamb to acute and chronic hypoxia are stressed.

Chapter 3

The reproducibility of Doppler flow velocity waveform recording and analysis was studied in 42 patients. The recording technique for blood flow velocity waveforms at the fetal cardiac level is described. Flow velocity waveforms from the fetal ascending aorta, pulmonary artery, and ductus arteriosus were characterized by the following angle-dependent parameters: peak systolic velocity (PSV), acceleration time (ACT), acceleration velocity (ACV), average velocity (AV) and, flow velocity integral (FVI). Nested analysis of variance was used to separate the sources of variation; variation between patients, repeated measurements (time interval 15 min) and tracing of flow velocity waveforms. For the ACT the variation between the consecutive tests was considerable. For the ACV a poor reproducibility was achieved for both recording and analysis. Several explanations are offered, among which are the relatively long fast Fourier transit

time of 20 ms and the steep ascending limb of cardiac flow velocity waveforms. There is a high reproducibility of both recording and analysis for the parameters PSV, AV and FVI. It is concluded that the PSV, AV, and FVI can be used for the assessment of fetal cardiac function.

Chapter 4

Animal experimental work and human Doppler studies have shown the redistribution of blood flow occurring in the growth-retarded fetus, with pre-ferential blood supply to the brain. In this chapter cardiovascular changes in the growth-retarded human fetus at different levels of the fetal circulatory system by Doppler ultrasound was studied.

In the first paper Doppler flow velocity waveforms from the internal carotid artery and basal arteries (middle cerebral artery, posterior cerebral artery and anterior cerebral artery) were documented in normal pregnancies and pregnancies complicated by intrauterine growth retardation. In normal pregnancy, both in the internal carotid artery and basal arteries a reduction in PI was documented during the last weeks of pregnancies in normal pregnancy. In IUGR, in all vessels a marked reduction in PI was observed, suggesting that all vessels studied participate in the circulatory redistribution favouring brain perfusion in the presence of chronic fetal hypoxia. No conclusion regarding differences in sensitivity and specificity could be drawn due to the limited number of flow velocity waveforms of the various cerebral vessels from pregnancies complicated by IUGR.

In the second paper flow velocity waveforms obtained at cardiac and peripheral level from 25 pregnancies complicated by IUGR were compared with those from 25 normal control subjects matched for gestational age and maternal parity. Normal pregnancy was characterized by high-forward velocity levels maintained throughout end-diastole at peripheral level. In IUGR, reduced end-diastolic velocities in the fetal descending aorta, umbilical artery, and maternal utero-placental artery were documented, suggesting raised umbilical placental and uteroplacental vascular resistance. Raised end-diastolic velocities were observed in the internal carotid artery, suggesting a brain-sparing effect. A significant correlation was found between the percentage of placental infarction and the PI from the umbilical artery and the EDV/PSV ratio from the maternal uteroplacental artery. The markedly reduced peak systolic velocities in the ascending aorta, pulmonary artery and ductus arteriosus observed in pregnancies complicated by IUGR, may be secondary to reduced volume flow, increased valve or vessel size, or raised afterload.

In the final paper, attention was focused upon the fetal cardiac outflow tract, both in normal pregnancy and IUGR. Peak systolic velocity in the ascending aorta and pulmonary artery increased linearly with advancing gestational age in the second half of normal pregnancy. Whereas in the pulmonary artery nearly

all peak systolic velocities were below the 5th percentile in IUGR, this was only 57% for peak systolic velocities in the ascending aorta. This may be explained by the fact that the afterload to the left ventricle may not only be determined by the umbilical placental and uteroplacental resistance but also by the resistance at cerebral level which is reduced in IUGR. In IUGR, the peak systolic velocities from both cardiac vessels were not related to fetal well-being as expressed by the Apgar score at 1 minute and the umbilical cord pH.

Chapter 5

The majority of reports regarding the relation between umbilical flow velocity waveforms and pregnancy outcome suggest a future role for umbilical artery recording as a secondary test for identifying fetuses at risk. In this chapter, Doppler flow measurements from the ascending aorta (AO), pulmonary artery (PA), umbilical artery (UA) and internal carotid artery (ICA), performed at 2-3 day intervals were related to the incidence of fetal distress and neonatal outcome. At peripheral level the pulsatility Index (PI) was calculated, whereas at cardiac level the peak systolic velocity (PSV) and time-average velocity (AV) were calculated. In all statistical analyses adjustments were made for gestational age as the Doppler parameters were gestational age dependent.

In the first paper, the monitoring value of the Doppler flow velocity waveforms in the development of fetal distress was studied in a longitudinal study design. Daily fetal heart rate monitoring was considered as the standard for assessment of fetal well-being, whereby fetal distress was defined as a Fischer score of $\leqslant 6$. Doppler flow velocity waveforms from UA (PI) and AO (PSV) were significantly related with the occurrence of fetal distress at the day of entry into the study. Doppler flow velocity waveforms from UA (PI), ICA (PI), and AO (PSV,AV), expressed as standard deviation scores (score), were significantly related to the incidence of fetal distress during follow up. After simultaneous assessment, this relation remained only significant for the peripheral arteries (UA and ICA). The multivariate assessment of the PIUA and PIICA scores resulted in a prognostic index for the development of fetal distress during follow up: $0.43 \times$ PIUA score $- 0.96 \times$ PIICA score. The life table constructed from data from women who had once during follow up an index value above the introduced cut-off level showed that nearly 50% of women developed fetal distress within a period of 1 week after the day on which their index value first became abnormal. The discriminative power of this prognostic index is demonstrated by the low percentage (13%) of abnormal index values in women who did not develop fetal distress (n=13), and the high percentage (71% when only the last 3 index values prior to fetal distress were considered) in women who did develop fetal distress (n=14). This study indicates the potential clinical value of the umbilical artery and internal carotid artery blood flow velocity waveforms for predicting fetal distress.

In the second paper, the last Doppler recording before delivery was related to neonatal outcome in the same study group. Neonatal outcome was determined by: Apgar score at 1 minute, umbilical artery acid-base status and oxygen tension (pO_2), number of nucleated red blood cells (NRBC), duration of ventilatory support, and sonographic appearance of cerebral leukomalacia. The time delay between the last Doppler measurement and delivery varied between 0 and 6 days (median, 1). Also here, gestational age was taken into account in the analysis. There was no relationship between Apgar score, acid-base status and Doppler parameters. Low AVAO was related to a low umbilical artery pO_2. Significant correlations were established between PSVPA, AVPA and PIUA, and the duration of neonatal ventilatory support. Infants who died within 22 days after admission to the neonatal intensive care unit (n=7) displayed a significantly higher PIUA than those who remained alive. The PIUA was also related to the absolute and relative number of NRBCs. No relationship existed between the Doppler parameters and degree of leukomalacia. It is concluded that from all Doppler parameters, the PIUA is most clearly related to neonatal outcome in IUGR.

Samenvatting

Hoofdstuk 1

Intrauterine groeivertraging (IUGR) is een belangrijke oorzaak van perinatale morbiditeit en mortaliteit en vormt daarom een belangrijk obstetrisch probleem. Ondanks het feit dat verschillende methoden beschikbaar zijn voor diagnose en monitoring blijft het antenataal vaststellen van IUGR moeilijk en onnauwkeurig. Uit dierexperimenteel onderzoek is gebleken dat er een hemodynamische redistributie plaats vindt in IUGR. Met behulp van Doppler ultrageluidsmetingen zou deze hemodynamische redistributie bestudeerd kunnen worden. Het doel van het beschreven onderzoek was veranderingen in Doppler bloedstroomsnelheidscurven op foetaal cardiaal en perifeer niveau vast te leggen en deze te relateren aan veranderingen in het foetale cardiotocogram en de neonatale toestand. Tevens wordt de reproduceerbaarheid van foetale cardiale bloedstroomsnelheidscurven bepaald.

Hoofdstuk 2

In dit hoofdstuk worden methodologische en dierexperimentele aspecten van de foetale hemodynamica behandelt. Problemen die zich voordoen bij kwantitatieve en kwalitatieve toepassingen van Doppler ultrageluid worden uiteengezet. Ook worden (patho)fysiologische mechanismen die ten grondslag liggen aan veranderingen in Doppler bloedstroomsnelheidscurven besproken. In het tweede deel van dit hoofdstuk worden bevindingen van dierexperimentele studies gepresenteerd. Hierbij is de aandacht gericht is op hemodynamische responsen van het foetale lam op acute en chronische stress.

Hoofdstuk 3

De reproduceerbaarheid van de registratie en analyse van Doppler bloedstroomsnelheidscurven werd bestudeerd bij 42 patienten. Tevens wordt de registratietechniek van bloedstroomsnelheidscurven op cardiaal niveau beschreven. Bloedstroomsnelheidscurven van de foetale aorta ascendens, arteria pulmonalis en ductus arteriosus werden gekarakteriseerd door de volgende hoek-onafhankelijke parameters: piek systolische snelheid (PSV), acceleratie tijd (ACT), acceleratie snelheid (ACV), gemiddelde snelheid (AV) en flow integraal (FVI). Geneste variantie analyse werd toegepast om de verschillende bronnen van variatie te scheiden; variatie tussen patienten, herhaalde metingen (tijdsinterval 15 min) en het natrekken van de bloedstroomsnelheidscurven. De variatie tussen de

opeenvolgende testen was aanzienlijk voor de ACT. De reproduceerbaarheid voor de ACV bleek slecht te zijn, zowel voor het registreren als voor de analyse. Verschillende verklaringen worden naar voren gebracht, waaronder de relatief lange Fourier transformatie tijd van 20 ms en het steile ascenderende deel van de cardiale bloedstroomsnelheidscurven. Er werd een goede reproduceerbaarheid verkregen voor de parameters PSV, AV en FVI. Geconcludeerd wordt dat de parameters PSV, AV en FVI gebruikt kunnen worden om de foetale hartfunctie te bestuderen.

Hoofdstuk 4

Bevindingen verkregen in dierexperimenteel onderzoek en humaan Doppler onderzoek duiden op een circulatoire redistributie in de groeivertraagde foetus. Hierbij treedt een preferentiële bloedtoevoer op naar de hersenen. In dit hoofdstuk werden de cardiovasculaire veranderingen met behulp van Doppler ultrageluidsmetingen op verschillende niveaus van het circulatoire systeem in de groeivertraagde humane foetus bestudeerd.

In het eerste artikel werden Doppler bloedstroomsnelheidscurven afkomstig van de arteria carotis interna en basale arteriën (arteria cerebralis media, arteria cerebralis posterior, en arteria cerebralis anterior) geregistreerd bij ongestoorde zwangerschappen en zwangerschappen gecompliceerd door IUGR. Bij ongestoorde zwangerschappen werd tijdens de laatste weken van de zwangerschap een afname gezien in de PI in de arteria carotis interna en basale arteriën. Bij zwangerschappen gecompliceerd door IUGR werd in alle vaten een duidelijke afname in PI gezien. Dit suggereert een circulatoire redistributie naar de hersenen, waarbij alle in dit onderzoek bestudeerde vaten betrokken zijn. Het beperkte aantal registraties in de verschillende cerebrale vaten maakte het niet mogelijk conclusies te trekken ten aanzien van verschillen in sensitiviteit en specificiteit.

In het tweede artikel werden perifere en cardiale bloedstroomsnelheidscurven van 25 zwangeren met IUGR vergeleken met 25 normaal zwangeren gematched op zwangerschapsduur en pariteit. De ongestoorde zwangerschap werd gekarakteriseerd door relatief hoge voorwaartse bloedstroomsnelheden gedurende de gehele diastole in de perifere vaten. Bij IUGR werd een afname in eind-diastolische snelheid gezien in de foetale aorta descendens, arteria umbilicalis en maternale utero-placentaire arteriën. Dit suggereert een verhoogde umbilico-placentaire en utero-placentaire vasculaire weerstand. Verhoogde eind-diastolische snelheden werden gezien in de arteria carotis interna. Dit suggereert een zogenaamd hersensparend effect. Er werd een significante correlatie gevonden tussen de mate van infarcering van de placenta en de PI van de arteria umbilicalis alsmede voor de eind-diastolische over piek systolische snelheid van de maternale utero-placentaire arteriën. De duidelijk verlaagde piek systolische snelheden die geregistreerd werden in de aorta ascendens, arteria pulmonalis en ductus arteriosus bij zwangerschappen gecompliceerd door IUGR zouden een gevolg kunnen zijn

van afgenomen volume flow, toegenomen klep of vaat diameter of verhoogde afterload.

In het laatste artikel staat de foetale cardiale outflow tract centraal, bij normaal zwangeren en zwangeren met IUGR. De piek systolische snelheid in de aorta ascendens en de arteria pulmonalis steeg lineair met toenemende zwangerschaps-duur in de tweede helft van de ongestoorde zwangerschap. Bijna alle piek systolische snelheden in de arteria pulmonalis lagen beneden de 5de percentiel, terwijl slechts 57% van de piek systolische snelheden in de aorta ascendens beneden de 5de percentiel lagen bij de zwangeren met IUGR. Dit zou verklaard kunnen worden doordat de afterload van de linker ventrikel niet alleen bepaald wordt door de umbilico-placentaire en utero-placentaire weerstand, maar ook door de weerstand op cerebraal niveau, welke verlaagd is bij IUGR. Bij IUGR waren de piek systolische snelheden van beide cardiale vaten niet gerelateerd aan de foetale toestand, gekarakteriseerd door de Apgar score na 1 minuut en de navelstreng pH.

Hoofdstuk 5

Het merendeel van de publikaties over de relatie tussen umbilicale bloed-stroomsnelheidscurven en foetale of neonatale toestand zien een toekomstige rol voor Doppler ultrageluidsmetingen als secundaire test ter identifikatie van foetussen "at risk" weggelegd.

In dit hoofdstuk werden Doppler ultrageluidsmetingen in de foetale aorta ascendens (AO), arteria pulmonalis (PA), arteria umbilicalis (UA) en arteria carotis interna (ICA) die drie maal per week verricht werden, gerelateerd aan de incidentie van foetale nood en de neonatale toestand. Voor de perifere bloed-stroomsnelheidscurven werd de PI berekend en voor de cardiale bloedstroom-snelheidscurven werd de piek systolische snelheid (PSV) en gemiddelde snelheid (AV) berekend. Bij alle statistische analyses werd gecorrigeerd voor de zwan-gerschapsduur omdat alle Doppler parameters afhankelijk waren van de zwan-gerschapsduur.

In het eerste artikel werd bij een longitudinale studie opzet de waarde van Doppler bloedstroomsnelheidscurven als monitoring methode voor de ontwik-keling van foetale nood bestudeerd. Als standaard voor het beoordelen van het foetale welzijn gold het dagelijks geregistreerde foetale hartfrequentiepatroon. Hierbij werd foetale nood gedefineerd als een Fischer score van ≤ 6 voor het foetale hartfrequentie patroon. Doppler bloedstroomsnelheidscurven van de UA (PI) en AO (PSV) waren significant gerelateerd aan het optreden van foetale nood op de dag van binnenkomst in de studie. Doppler bloedstroomsnelheids-curven van de UA (PI), ICA (PI) en AO (PSV, AV) uitgedrukt in standaard deviatie scores (score), waren significant gerelateerd aan de incidentie van foetale nood tijdens follow up. Bij gelijktijdige analyse bleef deze relatie alleen significant voor de perifere arteriën (UA en ICA). De multivariate analyse van de PIUA

en PIICA scores resulteerde in een prognostische index voor de ontwikkeling van foetale nood tijdens follow up: $0.43 \times$ PIUA score $- 0.96 \times$ PIICA score. Een life-table werd geconstrueerd met behulp van data van zwangeren die eens gedurende follow up een index waarde boven het geïntroduceerde cut-off niveau hadden. Deze life table liet zien dat bijna 50% van de zwangeren foetale nood ontwikkelden binnen één week na de dag waarop hun index waarde voor het eerst boven het cut-off niveau kwam te liggen. De discriminatieve waarde van de deze prognostische index volgt uit het lage percentage (13%) van abnormale index waarden bij zwangeren die geen foetale nood ontwikkelden (n=13) en het hoge percentage (71% wanneer alleen de drie laatste index waarden voorafgaand aan foetale nood in overweging genomen worden) bij zwangeren die foetale nood ontwikkelden (n=14). Deze studie duidt op een mogelijk klinische waarde van Doppler bloedstroomsnelheidscurven van de arteria umbilicalis en arteria carotis interna voor het voorspellen van foetale nood.

In het tweede artikel werd bij dezelfde studie populatie de laatste Doppler registratie voor de partus gerelateerd aan de neonatale toestand. Hierbij werd de neonatale toestand als volgt vastgelegd: Apgar score na 1 minuut, navelstreng zuur-base evenwicht en zuurstofspanning (pO_2), aantal kernhoudende rode bloedcellen, beademingsduur en echografisch gedetecteerde cerebrale leukomalacie. Het tijdsinterval tussen de laatste Doppler registratie en partus varieerde tussen 0 en 6 dagen (mediaan, 1). Ook hier werd in de analyse de zwangerschapsduur opgenomen. Er was geen significante relatie tussen de Apgar score, zuur-base evenwicht en de Doppler parameters. Een lage AVAO was gerelateerd aan een lage navelstreng pO_2. Significante relaties werden gezien tussen PSVPA, AVPA en PIUA, en de beademingsduur. Neonaten, die binnen 22 dagen na verwijzing naar de neonatale intensive care unit overleden, hadden een significant hogere PIUA dan degenen die in leven bleven. De PIUA was ook gerelateerd aan het absolute en relatieve aantal kernhoudende rode bloedcellen. Er werd geen relatie gezien tussen de Doppler parameters en het optreden van leukomalacie. Geconcludeerd wordt dat van alle Doppler parameters, de PIUA het meest duidelijk gerelateerd is aan de neonatale toestand bij IUGR.

Acknowledgements

Curriculum Vitae

1961   geboren te Dubbeldam

1979   eindexamen aan de scholengemeenschap College de Klop, Utrecht.

1979   inschrijving aan de Erasmus Universiteit Rotterdam.

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1987   onderzoeker in opleiding in dienst van de Nederlandse Organisatie voor Wetenschappelijk Onderzoek, o.l.v. Prof. dr J.W. Wladimiroff werkzaam binnen de afdeling verloskunde /gynecologie Dijkzigt ziekenhuis, Erasmus Universiteit Rotterdam (hoofd Prof. dr A.C. Drogendijk).

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