A DOPPLER ULTRASOUND STUDY OF HUMAN FETAL VASCULAR DYNAMICS

EEN DOPPLER ULTRAGELUIDSONDERZOEK NAAR DE BLOEDDOORSTROMING IN DE HUMANE FOETUS

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. A.H.G. RINNOOY KAN
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 14 JANUARI 1987 TE 14.00 UUR

DOOR

HILDA MARGARET TONGE

GEBOREN TE WELSHPOOL, WALES

1987
DRUKKERIJ J.H. PASMANS B.V., 's-GRAVENHAGE

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Chapter 1

INTRODUCTION

1.1 Historical background

It is not possible to understand the normal course of the fetal circulation from a knowledge of the anatomy of the fetal cardiovascular system alone. It is for this reason that it has taken several centuries to establish the direction of blood flow in the fetus, and it is only in the last thirty years that quantitative measurements of fetal blood flow have been available, predominantly from animal experimental studies.

An interest in the fetal cardiovascular system was expressed as early as the 2nd century A.D., when Galen of Pergamon described the connection of the umbilical cord with the fetus (Dobson, 1925). Leonardo da Vinci (1452-1519) also recognised the fetoplacental unit when he stated "The veins of the child do not ramify in the substance of the uterus of the mother but in the placenta, which takes the place of a shirt in the interior of the uterus, which it coats and to which it is connected but not united" (Da Vinci, 15th century). It took until the seventeenth century to prove that this was indeed the case.

The seventeenth century has been called the "age of physiology" because of the documentation and "discovery" of the circulation of blood by William Harvey in 1628. In his writings, Harvey accurately described the right to left vascular shunts, namely the foramen ovale and ductus arteriosus, that are present in the fetus, and their closure after birth (Harvey, 1628).

In 1778, Sabatier proposed that there was preferential distribution of well oxygenated blood to the ascending aorta to supply the brain and heart, and that there was no mixing of well oxygenated blood returning from the placenta with poorly oxygenated blood returning from the fetal tissues (Sabatier, 1778). The exact situation was not clarified until the 1920s and 1930s, when animal studies began to unfold the degree of mixing and oxygenation of major fetal vessels. Huggett in 1927, using fetal goats, demonstrated that the oxygen content in the carotid artery was greater than that in the descending aorta and umbilical artery (Huggett, 1927). Using cineangiographic methods, Barclay and co-workers illustrated the normal course of blood flow in the fetal lamb (Barclay et al, 1939). The extent of mixing of the fetal venous blood streams in the heart and great vessels, that are of widely differing oxygen content, was finally settled using the same radiographic technique by Sir Joseph Barcroft (1946). The degree of mixing was indeed incomplete but more complete than Sabatier supposed (Dawes, 1968). The results showed that poorly oxygenated blood returning from the fetal tissues was well mixed with well oxygenated blood from the placenta (Born et al, 1954). Using cineangiographic techniques also, Lind and Wegelius (1954) showed that the course of the human fetal circulation was essentially the same as that of the fetal lamb. Quantitative measurements of fetal blood flow steadily began to emerge from the 1950s onwards.

Improvements in experimental methods, such as better anaesthesia and the introduction of "chronic fetal preparations", provided more physiological and subsequently more reliable measurements of cardiac output and its distribution (Meschia et al, 1965). By the late sixties, therefore, a detailed account of fetal cardiac output and its distribution, fetal arterial blood pressure and cardiovascular control, together with other aspects of the fetal cardiovascular system was available (Dawes, 1968). The experimental studies outlined and described by Dawes give fundamental information in the field of fetal and neonatal physiology. Assali et al (1965) and Stembera et al (1964) were two other major contributory groups in the 1960s to the field of fetal blood flow with their studies on fetal cardiovascular dynamics (Assali et al, 1965; Stembera et al, 1965).
Heymann, Creasy and Rudolph in 1973 charted the blood flow (ml $kg^{-1}min^{-1}$) in a diagram of the fetal cardiovascular system for the mature fetal lamb, illustrating the high umbilical blood flow (41%) on the fetal side of the placenta (Cohn et al, 1974). Approximately 3.5% of the cardiac output in this study went to the brain. As humans have a larger brain (10% to 13% of weight at birth) it would be appropriate to assume that the percentage blood flow to the brain is higher in mature human fetuses than that of other animal species. The human fetus, due to its inaccessibility, could not be studied to the same extent until the introduction of high resolution ultrasound imaging.
Our knowledge of the human fetal cardiovascular system rapidly expanded in the seventies. As before, features of anatomy of the fetal cardiovascular system were the first to be studied together with functional aspects (Winsberg, 1972; Baars and Merkus, 1977; Wladimiroff et al, 1977). Quantitative measurements of fetal blood flow could only be performed after the introduction of Doppler ultrasound. The Doppler effect was the term given to the shifts in red light from binary stars. It was described by Christian Johann Doppler (an Austrian professor of mathematics and geometry) in 1842. Dr. Buys Ballot later in the same decade applied the Doppler effect to sound (Buys Ballot, 1845). In 1956, Satomura first realised that red blood cells can reflect ultrasound waves that are subject to a change in frequency in accordance with the Doppler effect (Satomura, 1956). His work and that of earlier investigators who used Doppler equipment applied the Doppler effect to adult cardiology. When Doppler ultrasound equipment was combined with two dimensional real time echo ultrasound, estimations of volume blood flow in the human fetus became possible (Gill and Kossoff, 1979; Eik-Nes et al, 1980).

It is because of a fundamental interest in fetal physiology and in particular the physiology of the fetal cardiovascular system that the studies presented in this thesis were performed. An understanding of the fetal circulation is important and essential in the care of the unborn child.

1.2 **Objectives**

The objectives of the study were fourfold:
The first objective was to obtain a non-invasive method of measuring volume blood flow in the lower thoracic level of the human fetal descending aorta with particular emphasis on pulsatile changes in the blood flow velocity and vessel diameter.
A discussion on technical and methodological aspects of volume blood flow measurements can be found in the second chapter.

Having studied the technical and methodological aspects of volume blood flow measurements in the descending aorta of the human fetus, and becoming more aware of the major limitations of such ultrasonic measurements, the second objective was to investigate and to collect data on normal pregnancy in the third trimester. The data from an initial study of twenty patients can be found in the third chapter.

A cardiac arrhythmia alters the "milieu interieur" and the adjustments that the human fetal cardiovascular system makes are of physiological importance. By investigating volume blood flow in the human fetus in the presence of an arrhythmia, our third objective was to elucidate the compensatory mechanisms that occur in the human fetus during such adverse conditions, and the data are presented in the fourth chapter.

Intrauterine growth retardation is a complication of pregnancy that is seen frequently in ante-natal clinics and on ante-natal wards. It also, unfortunately, tends to be a recurring problem for the expectant mother. The fourth objective was to investigate the changes that might occur in blood flow velocity waveforms in cases of intrauterine growth retardation and to assess the value of blood flow velocity waveform recordings for the early detection of such compromised fetuses. The data from these studies can be found in the fifth chapter.

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Chapter 2

TECHNICAL AND METHODOLOGICAL ASPECTS OF VOLUME BLOOD FLOW INVESTIGATIONS IN THE FETAL DESCENDING AORTA

Introductory remarks

Normal growth and well-being of the human fetus are dependent on a constant supply of oxygen and other nutritients, which is, in turn, dependent on normal blood supply. Quantitative information on human fetal blood flow is an essential adjunct, therefore, to our knowledge of fetal physiology and pathophysiology. So it is necessary to be able to measure as accurately as possible volume blood flow in the human fetus. The first paper describes and discusses the equipment and methods used and sources of errors encountered in our studies.

2.1 **Blood flow measurements in the fetal descending aorta: technique and clinics**

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Published in Clinical Cardiology, vol. 7, 323-329 (1984)

Summary

A combination of two-dimensional and real-time pulsed-Doppler ultrasound provides a non-invasive method of measuring human fetal blood flow without side effects. By not altering the physiological conditions of the fetus, it minimizes external stimuli that might affect blood flow. However, due to the inaccessibility of the vessels under investigation, errors from the ultrasound technique arise and these are still being assessed. Studies of fetal blood flow suggest that the fetal circulation has a low peripheral resistance and that the increase in blood flow found with increasing gestational age is due predominantly to the increase in the actual dimensions of the fetal vasculature. Investigations in abnormal pregnancies, such as small-for-dates and those with cardiac arrhythmias have shown that the fetal cardiovascular system is capable of compensating efficiently to maintain normal physiological condition, but only within the limits defined by the Frank Starling mechanism.

Key Words: 2-dimensional real-time ultrasound, Doppler ultrasound, human fetal blood flow, fetal descending aorta.

Introduction

Information on fetal blood flow has been obtained from animal studies (Comline and Silver, 1975; Dawes, 1968). Techniques used in these studies and others, for example, clearance rates measurements (Clavero et al, 1973; Gant et al, 1976), post-abortion (Assali et al, 1969) and post-delivery measurements (McCallum, 1977a,b; Stembera et al, 1968), were invasive and introduced non-physiological conditions that would certainly have influenced results.

Recently, non-invasive methods using two-dimensional real-time and continuous-wave or pulsed-wave Doppler ultrasound have been used to record blood flow velocity waveforms in the human fetus.

In 1977 FitzGerald and Drumm reported on the measurement of blood flow velocity in the umbilical cord by means of continuous-wave Doppler ultrasound. McCallum et al (1978) recorded blood flow velocity waveforms from the umbilical artery. Measurements on blood flow in the fetal descending aorta and umbilical vein using Doppler ultrasound were first described by Gill and Kossoff (1979) and by Eik-Nes et al (1980a).

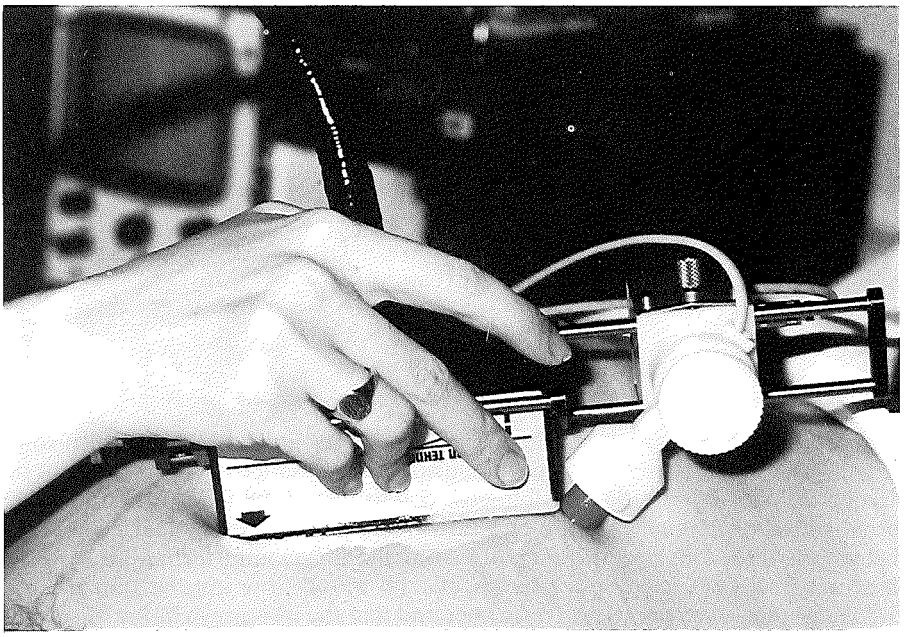

Figure 1. Photograph of linear array real-time transducer with Doppler probe attached at a fixed angle of 45°.

Specification of combined 2-D real-time and pulsed Doppler equipment

The system which will be described here was introduced by Eik-Nes et al (1980a,b). First the fetal descending aorta was located by means of a two-dimensional (2-D) dynamically focused linear array transducer (Fig. 1). The sound velocity calibration marks were set at 1540 m/s. The transducer frequency was 3.5 MHz, and the axial and lateral resolution were 1 and 3 mm, respectively. A 2 MHz pulsed-Doppler transducer with a diameter of 12 mm was used for measurement of the blood flow velocity. The ultrasound pulses were emitted with a duration of 10 μs each at a repetition frequency of 6.5 or 9.75 KHz, which allows measurement of velocities up to 1.7 m/s to a depth of 8.5 cm and velocities up to 1 m/s to a depth of 11.0 cm. The Doppler probe was attached to the linear array real-time transducer so that the Doppler beam intersected the fetal descending aorta at a fixed angle of 45° (Fig. 1). The beam direction with the sample gate position (electronic marker) could be displayed on the real-time screen. The Doppler shift (fd) is given by the equation:

$$fd = \frac{2\ fo\ v\ \cos\ \alpha}{c}$$

where fo is the ultrasound frequency, v is the velocity of the erythrocytes, c is the sound velocity in soft tissues (1540 m/s) and α the angle between the ultrasound beam and the direction of erythrocyte movement. The frequency shift of the reflected ultrasound will be increased in proportion to v. The reflected Doppler signals were fed into estimators of maximum and mean Doppler shifts, which produced analogue output voltages.

Due to an unacceptable interference, which results from simultaneous emission of ultrasound pulses from 2-D real-time and the Doppler pulses, we introduced an interface system. This reduces the image representation from 50 to 1 image per second by switching off the real-time for a period of 980 ms. During this period flow velocity in the fetal descending aorta can be measured. During the remaining 20 ms the pulsed-Doppler probe is switched off and the real-time scanner builds up an image; the last measured flow velocity is then contained by means of "hold circuits". This system thus allows instantaneous resetting of the sample volume relative to the vessel lumen, resulting in more accurate flow velocity measurements over a longer period of time.

Comments

The advantage of pulse-wave over continuous-wave Doppler is that the former is range selective. Each short pulse of ultrasound has to travel to the vessel and back. It should be realized that there is a depth limitation determined by the pulse repetition frequency (PRF). Moreover, the highest Doppler frequency which can be picked up without ambiguity is determined by PRF. Therefore peak maximum velocities up to 1.4 m/s in the fetal descending aorta can only be acurately recorded up to a depth of 11 cm when insonation angles of 45-50°, a PRF of 6.4 KHz and Doppler ultrasound frequencies of 2-3 MHz are employed.

Recording procedure:
Blood flow (Q) is calculated according to the equation:

$$Q = \frac{v \pi r^2}{\cos \alpha}$$

where v = blood flow velocity and r = vessel radius.
Following location and determination of vessel orientation, the following measurements are essential in the calculation of volume blood flow: (1) the flow velocity within the vessel; (2) vessel size.

Measurement of blood flow:
The first step was positioning the real-time transducer parallel to the aorta, ensuring maximum display of the vessel length on the real-time screen. An electronic marker representing the sample gate was subsequently moved along the path towards the intersection of the vessel above the diaphragm (descending thoracic aorta) (Fig. 2). The marker was then placed in the centre of the vessel and audio signals were used to ensure that the sample gate was covering the whole lumen of the vessel. A recording of the mean flow velocity was subsequently made.

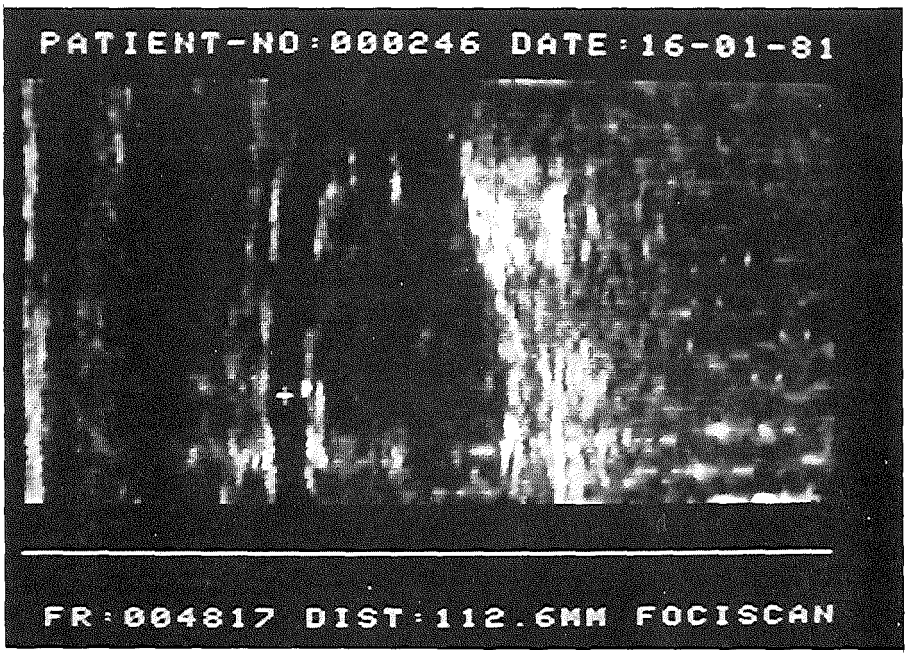

Figure 2. Photograph of the fetal descending aorta with the electronic marker, representing the sample gate, positioned in the centre of the vessel lumen.

Comments:
Mean flow velocity calculations are based upon the assumption that flow in major arterial vessels is laminar. Recently, Griffin et al (1983) pointed out that in the fetal descending thoracic aorta, blood flow depicts a plug profile during systolic acceleration and a parabolic profile during diastole. Measurement of mean blood flow velocity is subject to the following errors:

- Incorrect positioning of the real-time transducer relative to the longitudinal cross-section of the aorta. It has been established that when the angle (α) between the real-time and pulsed-Doppler transducer exceeds 60°, an error in flow velocity measurement of at least 20% can be expected (Griffin et al, 1983).
- Incorrect positioning of the sample gate. The sample gate should cover the entire lumen in order to make a correct measurement over the cross-sectional area of the vessel. In the present system this is feasible in vessels with diameters between 4 and 9 mm, which is the range usually encountered during the third trimester of pregnancy. Inappropriate positioning of the sample gate may result in erroneous information about flow velocity, because of the inclusion of other major vessel structures within the sample gate.
- Incorrect high-pass filters. High-pass filters are used to eliminate high intensity, low frequency Doppler signals originating from the pulsating aortic wall movements. Initially, the cut-off point was set at 600 Hz, resulting in considerable loss of frequency information during diastole. Now, a cut-off level at 150 Hz is generally accepted.

Measurement of vessel size:
Aortic diameter measurements have been carried out from 2-D real-time images (Eik-Nes et al, 1980; Griffin et al, 1983; Jouppila et al, 1983; Wladimiroff et al, 1981), M-mode (Eik-Nes et al, 1982) and time-distance recordings (TD) (Eik-Nes et al, 1984). Whereas the first method only provides fractional information on vessel size, the latter method allows continuous calculation of instantaneous flow in the cardiac cycle using the pulsatile velocity and diameter profiles (Tonge et al, 1983).

Comments:
Since errors in vessel diameter measurement will be squared when calculating volume blood flow, one should have detailed knowledge of the possible problems which one may encounter in the vessel measurement.

- Pulsatility of the arterial vessel wall. The pulsatility in aortic diameter can be a major source of error in volume flow measurements. We found that blood flow calculations based on the maximum vessel diameter may lead to a volume flow overestimation of 9%, whereas blood flow calculations based on a minimum vessel diameter may result in a volume flow underestimation of 19%. In practice this means that if a vessel diameter measurement is carried out from one frozen 2-D real-time image, the error in volume flow will vary between +9 and −19%; an underestimation of 5% is possible if ten randomly selected real-time images are taken. From M-mode recordings, in which usually the mean of the minimum and maximum diameter is taken, a volume flow underestimation of 5% can be expected.
- Origin of the vessel wall echoes. It is not known whether the echo-reflecting

boundary of the fetal aortic wall is determined by the muscular layer or by the surrounding connective tissue. In nearly all studies the vessel diameter is measured between the leading edges of echoes from the proximal and distal vessel wall. We found an overestimate in volume blood flow of 8% when the muscular layer alone was taken into account, and an overestimate of 11.5% when both muscular and surrounding tissue were considered.

Clinical data

Normal pregnancy:

Blood flow in the fetal descending aorta has been studied during the third trimester of pregnancy. The mean blood flow velocity was measured at the lower thoracic level of the descending aorta. The pulsatile vessel diameter was registered at the same level using the dual-time distance recorder. Simultaneous recording of blood flow velocity pulsatile diameter was not possible due to the interference between the ultrasound signals from the real-time and Doppler transducers. Instead, these profiles were compared in cardiac cycles of equal R-R intervals as obtained by an external and fetal ECG (Fig. 3) (Tonge et al, 1983). Note that the blood flow velocity profile is above the baseline throughout the cardiac cycle. For each of these cardiac cycles, the following parameters were established: (1) Mean blood flow velocity profile: i.e., peak mean velocity and time averaged mean velocity (cm s^{-1}), and acceleration of mean flow velocity (cm s^{-2}). (2) Pulsatile diameter profile: diastolic diameter (mm), maximum diameter change i.e., diameter change at peak height of pulse wave (%) and rate of vessel wall expansion (cm s^{-1}). (3) Pulsatility index: trough to peak height divided by mean height over one cardiac cycle (PI). (4) Combined flow velocity and pulsatile diameter profile: pulsatile flow integrated over one cardiac cycle (i.e., aortic stroke volume). During one cardiac cycle the flow velocity and pulsatile diameter profiles were divided into equal periods. The blood flow velocity and vessel diameter were sampled at these periods and the flow velocity was subsequently calculated using the formula: $Q = 0.25 \times \pi \times d^2 \times v$, where Q = flow, d = diameter and v = angle corrected velocity, as $\cos \alpha = 1$.
In each patient data analysis took place during 10 cardiac cycles. A total of 34 normal pregnant subjects between 28 and 40 weeks of gestation were included in the study. Nine subjects were between 28 and 32 weeks (group I), 12 subjects were between 32 and 36 weeks (group II), and 13 subjects were between 37 and 40 weeks of gestation (group III). The actual data are presented as mean values ± SD in Table I.
Blood flow velocity profile, rate of vessel wall expansion, maximum diameter, and pulsatility index were not significantly different between these groups. A significant increase was observed for the descending aorta, aortic stroke volume, and average mean blood flow values from group I to group II (Student's *t*-test, $p < 0.05$).
The increase from group II to group III is only significant for the effective diameter of the descending aorta ($p < 0.05$).

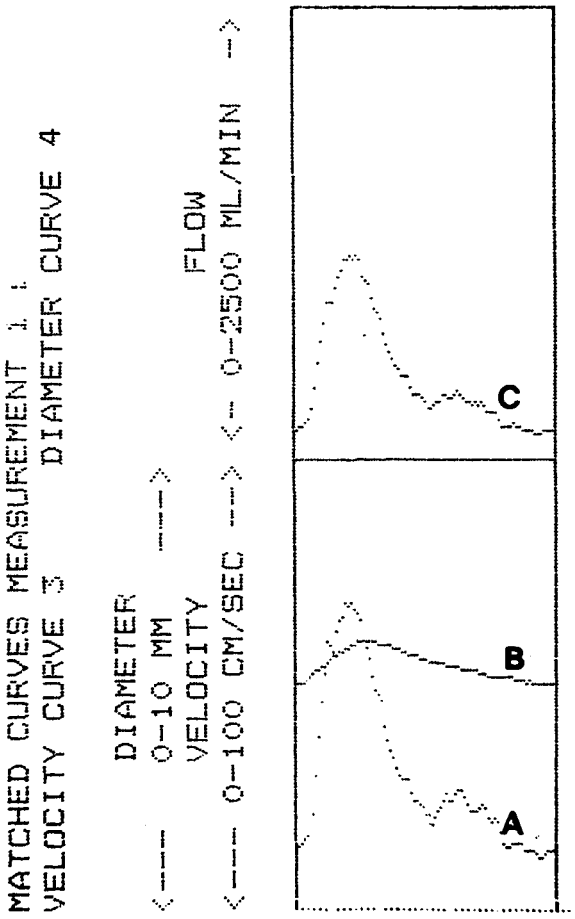

Figure 3. Tracings obtained of the mean blood flow velocity (A) and pulsatile diameter changes (B) over the cardiac cycle. C represents the mean blood flow over the cardiac cycle calculated from tracings A and B.

Table I. The results of the mean blood flow velocity profile, pulsatile diameter profile and combined blood flow velocity and pulsatile diameter profiles for groups I, II and III.

	Group I (28-32 wk, n=9)	Group II (33-36 wk, n=12)	Group III (37-40 wk, n=13)
Peak mean velocity (cm s^{-1})	70.4 ± 7.3	73.2 ± 7.5	76.0 ± 11.2
Time-averaged mean velocity (cm s^{-1})	27.0 ± 4.2	28.7 ± 5.3	26.5 ± 5.0
Flow velocity acceleration (cm s^{-2})	2022 ± 574	2550 ± 767	2087 ± 605
Effective diameter (cm)	0.56 ± 0.06	0.64 ± 0.07	0.70 ± 0.06
Diameter change (%)	13.9 ± 4.4	14.8 ± 2.8	12.9 ± 5.0
Rate of vessel wall expansion (cm s^{-1})	2.0 ± 0.4	2.2 ± 0.7	2.1 ± 0.9
Pulsatility index	2.6 ± 0.3	2.6 ± 0.3	2.8 ± 0.3
Mean volume blood flow (ml min^{-1})	392 ± 123	553 ± 149	621 ± 144
Stroke volume (ml)	2.7 ± 0.9	3.9 ± 1.2	4.4 ± 1.1

Comments:
The blood flow velocity waveform is biphasic with a systolic peak and forward flow during diastole. The end-diastolic forward flow indicates continuous perfusion as a result of the low placental resistance. The relative constancy of the PI as a measure of placental flow resistance has also been reported by Griffin et al (1983) and Lingman et al (1983). The constancy of the mean blood flow velocity observed by us and others (Griffin et al, 1983; Maršál et al, 1984) indicates that the rise in volume blood flow in the fetal descending aorta during the third trimester of pregnancy is solely determined by the increase in cardiac ventricular and aortic vessel size. The blood flow figures in Table I are in agreement with those provided by Griffin et al (1983) and Maršál et al (1984) and are significantly higher than the figures of 365 $\pm$ 90 (SD) ml at 27-33 weeks and 490 $\pm$ 65 (SD) ml at 34-41 weeks, reported in an earlier study (Wladimiroff et al, 1981a).
This difference is determined by the lowering of the cut-off level of the high pass filters from 600 to 150 Hz. In vitro and sheep experiments carried out with present Doppler equipment in our laboratory have indicated that the volume blood flow calculations as presented in Table I should be considered with caution (Struijk et al, 1985). The large standard deviations of the mean blood flow values are not only determined by the grouping of data over several gestational weeks, but also by the limited accuracy of the Doppler technique as a result of the pitfalls described earlier.
An additional inaccuracy is introduced by expressing blood flow figures per kilogram fetal weight, the latter being achieved from intrauterine ultrasound measurement of abdominal circumference (Campbell and Wilkin, 1975) or a combination of biparietal diameter and transverse abdomen measurements (Eik-Nes and Gröttum, 1982b).
From previous cardiac output data (Wladimiroff et al, 1981b, 1982) and blood flow data similar to those in Table I, Tonge et al (1983) estimated that the percentage of total cardiac output directed to the descending aorta varies between 65 and 80%. There seems to be general agreement now on the importance of flow velocity waveform analysis in complicated pregnancies. Lingman et al (1983) in a preliminary report described flow velocity waveforms in small-for-dates, which were characterized by a higher rising systolic slope and a very low diastolic flow. A similar observation was made by us in a case of ventricular tachycardia resulting in reduced cardiac output (Wladimiroff et al, 1983).

Internal and external stimuli affecting fetal blood flow

Several internal and external stimuli may affect fetal blood flow and therefore may lead to misinterpretation of collected data. Blood flow velocity in the fetal descending aorta is clearly modulated by fetal breathing movements (FBM). During FBM there are rhythmic changes in the flow velocity pattern, mainly during diastole, resulting in a mean velocity increase of about 16% (Maršál et al, 1984). External stimuli such as maternal smoking (Jouppila et al, 1983; Pijpers et al, 1984) and moderate maternal exercise (Pijpers et al, 1984) do not seem to affect fetal aortic blood flow. In a study of fetal cardiac arrhythmias (atrioventricular blocks and supraventricular tachycardias) we were able to confirm an earlier report by

Maršál et al (1982) that despite alterations in rhythm, blood flow in the fetal descending aorta is maintained within the normal range.

Comments:
The effect of fetal breathing movements has been extensively studied by Maršál et al (1984). They noticed an increase in umbilical venous blood flow velocity similar to that in the fetal descending aorta. Of interest is that during inspiration a distinct vessel elongation occurs in the umbilical vein, resulting in a diminished vessel diameter. Although no data are available, it is less likely that such an elongation occurs in the descending aorta because of its vessel wall structure.
It seems that the velocity changes observed in the umbilical vein and descending aorta are directly caused by the pressure changes during contractions of the diaphragm.
The compensatory alterations in fetal aortic blood flow during severe cardiac arrhythmia reflect changes in cardiac contraction force and clearly illustrate the presence of the Frank Starling mechanism in the human fetus. It also seems from our study that heart rates between 50 and 250 bpm are the functional limits of the fetal myocardium to this mechanism.
Blood flow measurements in the fetal descending aorta during fetal cardiac arrhythmias are becoming important in the assessment of fetal cardiac function, particularly when there is an associated structural cardiac defect (Stewart, 1983).

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Explanatory comments

A good quality fetal ECG is not always possible to obtain, particularly between 32 and 36 weeks gestation when there is a substantial amount of vernix caseosa present. An alternative method of comparing cardiac cycles from the blood flow velocity and pulsatile vessel diameter waveforms is therefore desirable. The following article describes such an alternative method and compares it with that of the fetal ECG.

2.2 The first derivative as a means of synchronizing pulsatile flow velocity and vessel diameter waveforms in the fetal descending aorta

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Summary

In order to calculate volume flow, blood flow velocity and pulsatile vessel diameter waveforms in the lower thoracic part of the descending aorta of the fetal lamb and human fetus were matched for identical cardiac cycle length by fetal ECG and the first derivative of these waveforms. Volume flow values were not essentially different using either method. There is simultaneous onset of the blood flow velocity and pulsatile vessel diameter waveforms. The first derivative can reliably replace the fetal ECG as a means of synchronising blood flow velocity and pulsatile vessel diameter waveforms in the fetal descending aorta.

Introduction

It has become increasingly clear that measurements of blood flow velocity and in particular the vessel diameter for estimating volume flow in the fetal descending aorta, are subject to a number of inaccuracies (Eik-Nes et al, 1982; Tonge et al, 1984). One of the important factors in the study of arterial volume flow is the pulsatility of both the flow velocity and vessel diameter profiles. Simultaneous recording of these profiles would allow the construction of a volume flow waveform which takes the pulsatile character of the vessel diameter into account. This is, however, impossible due to unacceptable interference between emitted pulses from real-time and Doppler transducers. An indirect solution to the problem is to compare blood flow velocity and pulsatile vessel diameter profiles in cardiac cycles of similar length as determined by the fetal ECG (Tonge et al, 1983; Lingman et al, 1986).

An optimal fetal ECG recording cannot always be obtained, even with present day fetal heart rate monitors. Therefore, we looked for an alternative method of synchronizing pulsatile blood flow velocity and vessel diameter waveforms in the fetal descending aorta that was not dependent on obtaining a fetal ECG.
The onset of both waveforms is almost simultaneous (Lingman et al, 1986). This information was applied to synchronise the two waveforms. To determine the onset of the cardiac cycles the first derivative of the blood flow velocity and pulsatile vessel diameter waveforms was used.
This paper presents a comparative study, where volume blood flow data obtained from the lower thoracic level of the fetal descending aorta was analysed initially by the original fetal ECG method (Tonge et al, 1983), and, secondly, re-analysed using the alternative method in which the first derivative is used for synchronisation.

Material and Methods

The comparative study was performed in a fetal lamb at 130 days (0.9) of gestation in the first instance. After induction of anaesthesia with ketamine hydrochloride (1000 mg), atropine (0.5 mg) and pentobarbital sodium (300 mg) intravenously, the ewe was intubated. An abdominal mid-line incision was made and the pregnant uterus was subsequently exposed. Throughout surgery the ewe was ventilated with a mixture of nitrous oxide (4:1) and oxygen (2:1) supplemented by enflurane (0.5-2 vol%).
In the second instance, the study was performed in a normal, non smoking human gravida of 37 weeks gestation (0.9), in a semi-recumbent position.
In both the fetal lamb and human fetus, the following three physiological signals were obtained:

- the pulsatile blood flow velocity waveform in the fetal descending aorta using a 2 MHz pulsed Doppler system (PEDOF) attached to a 3.12 MHz linear array real-time transducer (Organon Teknika). In the fetal lamb the real-time transducer was placed directly on the uterine wall.
- the pulsatile vessel diameter waveform in the fetal descending aorta using a 2 dual time-distance (TD) recorder. From the real-time image (Organon-Teknika) a line was selected and the markers of the TD recorder were positioned on the deflections of the A-mode representation of the proximal and distal vessel wall.
- the fetal ECG by means of an abdominal ECG monitor (HP-8040). From the maternal abdominal wall in the human study and from electrodes placed in the fetal hind legs in the lamb study. In the analogue output of the ECG monitor a block-shaped pulse indicated the R-top of the fetal ECG.

An Apple II microcomputer was used for data collection following analogue/digital conversion (AI 13, Interactive Structures Inc). All analogue signals were sampled for a fixed period of five seconds at a frequency of 200 Hz, resulting in 1000 samples for each signal and thus allowing a detailed description of each signal (Figs. 1 and 2). In the first derivative method, a rise in the upstroke of 750 (cm s^{-2}) for the blood flow velocity profile and of 6 mm s^{-1} for the pulsatile vessel diameter profile was arbitrarily selected for accepting a particular cardiac cycle (Figs. 1 and 2). The maximum rate of rise of the blood flow velocity and pulsatile vessel diameter waveforms was calculated as the peak (B) in the first derivative. The zero-

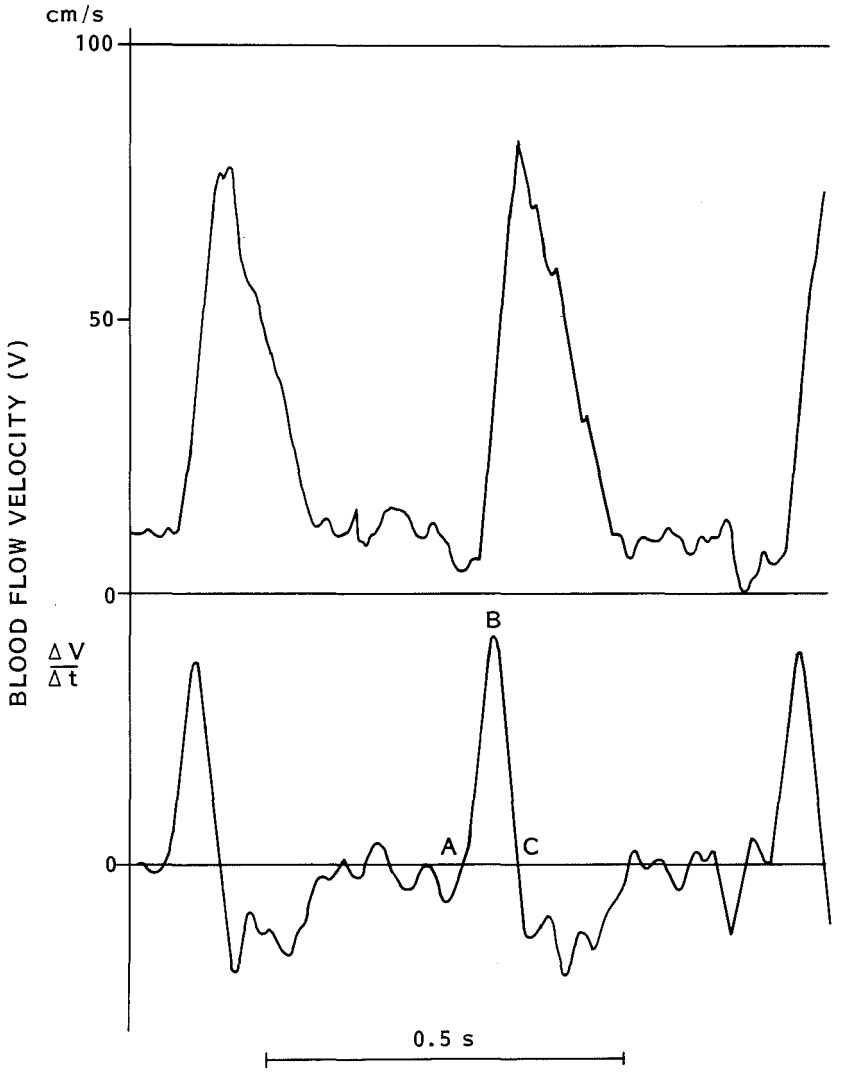

Figure 1. First derivative of the blood flow velocity waveform. A = onset of cardiac cycle; B = point of maximum rise in the waveform; C = peak velocity.

line crossing (A) preceding this peak was defined as the onset, the zero-line crossing (C) following the peak as the location of the peak in the original blood flow velocity and pulsatile vessel diameter waveforms.

Initially, matching of the blood flow velocity and pulsatile vessel diameter waveforms was carried-out using the R-R intervals of the fetal ECG. A difference in cardiac cycle length of 5% was the maximum tolerated discrepancy permitted for synchronization of the two waveforms. The following parameters were calculated:

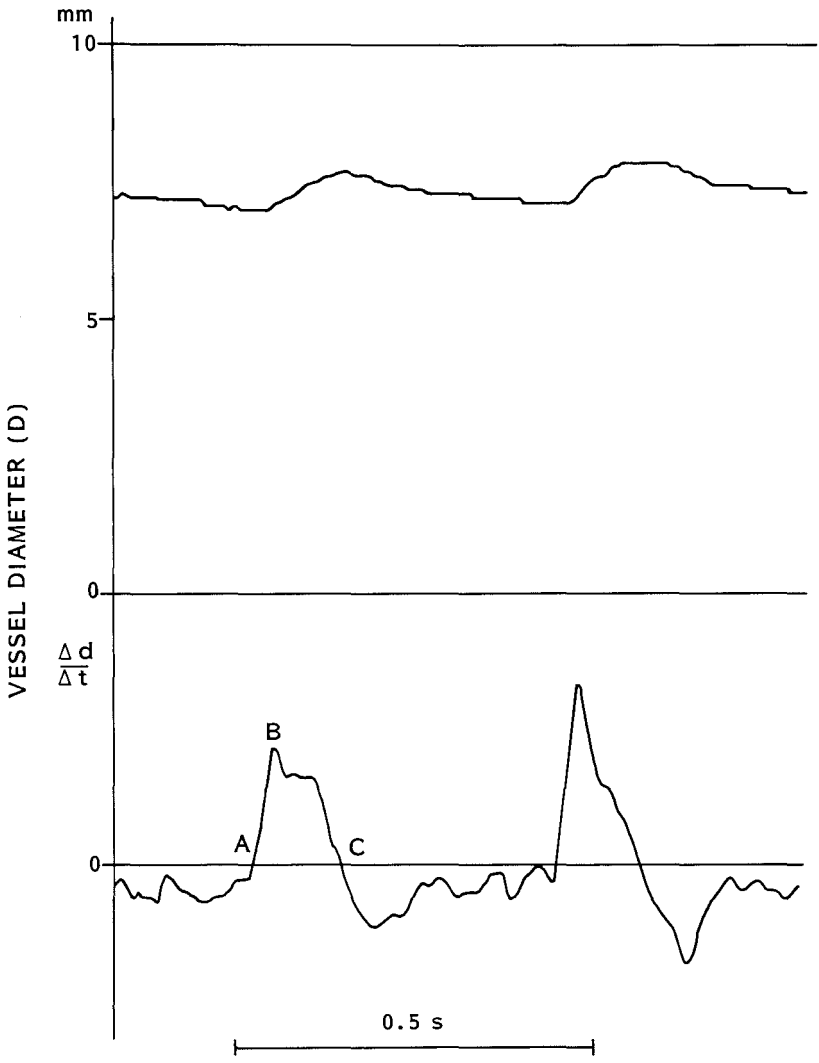

Figure 2. First derivative of the pulsatile vessel diameter waveform. A = onset of cardiac cycle; B = point of maximum rate of rise of the waveform; C = maximum diameter.

a. the pulsatile flow velocity waveform: lagtime between R-top fetal ECG and onset flow velocity waveform (ms), period time (ms), crest time (ms) = time interval between onset and peak velocity, velocity acceleration (cm s^{-2}), peak and end-diastolic velocities (cm s^{-1}), averaged velocity (cm s^{-1}) and pulsatility index (Gosling and King, 1975).
b. the pulsatile vessel diameter waveform: lagtime between R-top fetal ECG and onset vessel diameter waveform (ms), period time (ms), crest time (ms), expansion

velocity (mm s^{-1}), maximum and minimum diameters (mm) and averaged diameter (mm).
c. the volume flow profile: peak flow (ml min^{-1}), aortic stroke volume (ml), averaged volume flow (ml min^{-1}).
In the fetal lamb, a total of 33 cardiac cycles was matched. In the human fetus, the total was 10.
Having completed analysis using the fetal ECG, cardiac cycles were resynchronised applying the first derivative method. The cardiac cycles were matched using onset-to-onset intervals, and the same parameters were calculated.
For the fetal lamb, the selected velocity cycles were the same as those utilised for the fetal ECG matching. The computer selected, however, only 25 of the same diameter cycles that were utilised in the fetal ECG synchronisation. Similarly, for the human fetus, the velocity cycles were the same. The computer selected only 5 of the same diameter cycles that were utilised for the fetal ECG matching. The diameter cycles used for the first derivative synchronisation only were those cardiac cycles that were found to fit the criterium described earlier, where there was a 5% or less difference in cardiac cycle length.
Statistical analysis was performed using the paired student's *t*-test.

Results

Tables I and II present the data on blood flow velocity, pulsatile vessel diameter and volume flow (mean ± SD) calculated from the waveforms in the fetal lamb and human fetus.

Table I. Blood flow velocity, pulsatile vessel diameter and volume flow data at the lower thoracic level of the fetal descending aorta according to fetal ECG (FECG) and first derivative synchronized cardiac cycles in the fetal lamb.

	According to FECG		According to derivative method		
	x	SD	x	SD	% Difference
Velocity cycles:					
Lagtime R-Top FECG/onset FVWF (ms)	54	9	—	—	—
Crest time (ms)	84	12.5	84	12.5	0.0
Period time (ms)	308	25	305	24	-1.0
Peak velocity (cm s^{-1})	55.7	9.9	55.7	9.9	0.0
End diastolic velocity (cm $^{-1}$)	9.4	3.8	3.9	9.8	-58.5
Averaged velocity (cm s^{-1})	23.7	6.8	23.6	7.0	-0.4
Pulsatility Index	2.0	0.3	2.4	0.8	20.0
Velocity acceleration (cm s^{-2})	1112	170	1112	170	0.0
Diameter cycles:					
Lagtime R-Top FECG/onset VDWF (ms)	50	24	—	—	—
Crest time (ms)	113	22	116	18	-2.7
Period time (ms)	300	30	309	27	3.0
Maximum Diameter (mm)	7.5	0.4	7.5	0.4	0.0
Minimum Diameter (mm)	7.2	0.5	6.7	0.4	-6.9
Averaged Diameter (mm)	7.3	0.4	7.2	0.4	-1.4
Expansion Velocity (cm s^{-1})	8.9	2.3	8.8	2.4	-1.1
Calculated volume flow cycles:					
Averaged flow (ml min^{-1})	581	110	575	117	-1.0
Aortic stroke volume (ml)	2.9	0.4	2.9	0.4	0.0
Peak flow (ml min^{-1})	1439	130	1431	139	-0.6

FVWF = flow velocity waveform; VDWF = vessel diameter waveform.

Table II. Blood flow velocity, pulsatile vessel diameter and volume flow data at the lower thoracic level of the fetal descending aorta according to fetal ECG (FECG) and first derivative synchronized cardiac cycles in the human fetus.

	According to FECG		According to first derivative method		
	x	SD	x	SD	% Difference
Velocity cycles:					
Lagtime R-Top FECG/onset FVWF (ms)	46	12	—	—	—
Crest time (ms)	85	15	85	15	0.0
Period time (ms)	431	7	432	17	0.2
Peak velocity (cm s^{-1})	73.1	3.7	73.1	3.7	0.0
End diastolic velocity (cm $^{-1}$)	9.6	2.3	4.5	2.1	-53.1
Averaged velocity (cm s^{-1})	24.2	2.4	24.1	2.5	-0.4
Pulsatility Index	2.6	0.2	2.9	0.3	11.5
Velocity acceleration (cm s^{-2})	1673	194	1673	194	0.0
Diameter cycles:					
Lagtime R-Top FECG/onset VDWF (ms)	52	6	—	—	—
Crest time (ms)	118	12	125	11	5.9
Period time (ms)	431	7.4	437	13	1.4
Maximum Diameter (mm)	8	0.5	8.1	0.6	1.3
Minimum Diameter (mm)	7.6	0.5	7.4	0.5	-2.6
Averaged Diameter (mm)	7.8	0.5	7.7	0.5	-1.3
Expansion Velocity (cm s^{-1})	9.7	2.1	8.9	0.6	-8.2
Calculated volume flow cycles:					
Averaged flow (ml min^{-1})	729	143	702	130	-3.7
Aortic stroke volume (ml)	5.2	1.0	5.1	1.0	-1.9
Peak flow (ml min^{-1})	2254	315	2196	327	-2.6

FVWF = flow velocity waveform; VDWF = vessel diameter waveform.

According to the fetal ECG synchronisation, for the fetal lamb, the lagtime between the R-top fetal ECG and the onset of the blood flow velocity cardiac cycles was 54 ms, whereas the lagtime between the R-top fetal ECG and the onset of the pulsatile vessel diameter cardiac cycles was 50 ms. This is a difference of -4 ± 29 (SD) ms. Likewise, for the human fetus, this difference was $+6 \pm 13$ (SD) ms. These differences are not statistically significant.

The percentage differences in end diastolic velocities for the fetal lamb and human fetus between the first derivative synchronisation and fetal ECG synchronisation were -58.5 and -53.1 respectively. These are statistically significant values ($p < 0.01$). The pulsatility index value was therefore significantly higher in the fetal ECG cardiac cycles ($p < 0.01$). The percentage differences in minimum diameter for the fetal lamb and human fetus between both methods of matching were also statistically significant ($p < 0.01$). However, there was no statistically significant difference found for any of the other parameters, including volume flow calculations.

Discussion

The present study shows a good agreement between fetal ECG and "first derivative" synchronized cardiac cycles with respect to nearly all blood flow

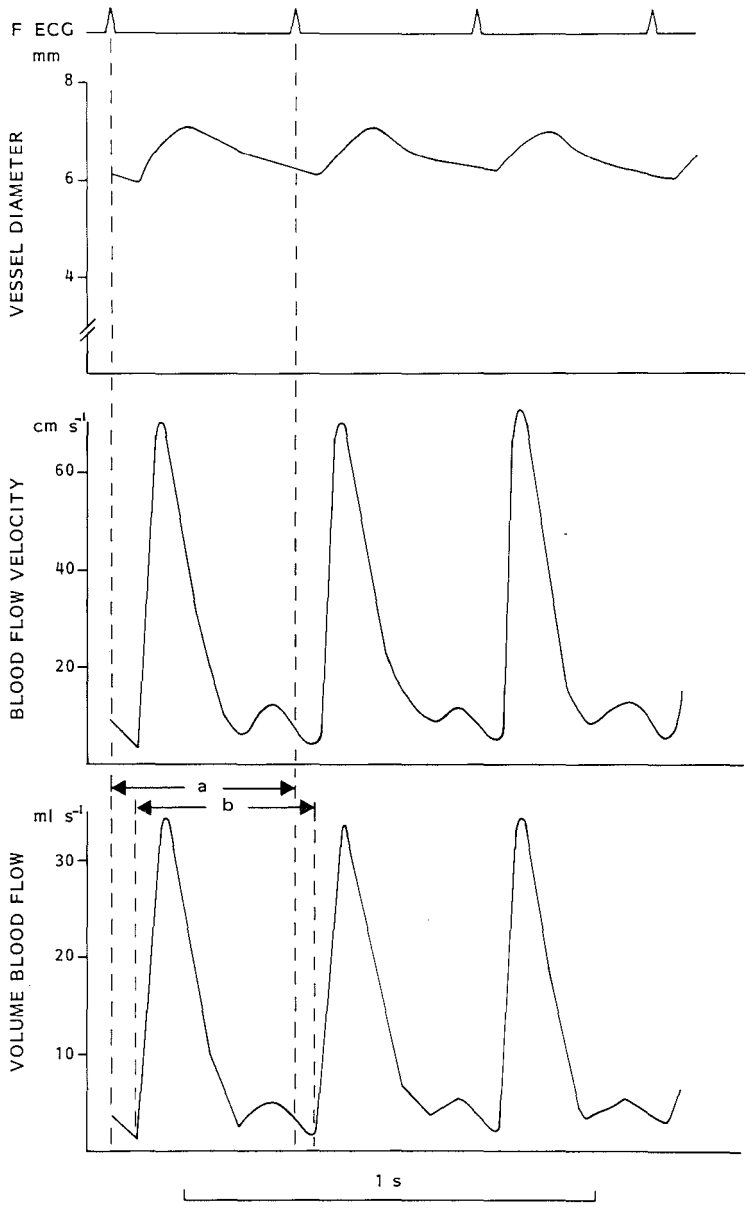

Figure 3. The synchronisation of the pulsatile vessel diameter and blood flow velocity waveforms by fetal ECG, from which volume blood flow waveforms can be constructed. (a-b) = lag time between fetal ECG and onset of the cardiac cycles for all waveforms.

velocity and pulsatile vessel diameter parameters both in the fetal lamb and human fetus.

Both in the fetal lamb and human fetus, the mean time lag between the onset of the blood flow velocity and pulsatile vessel diameter waveforms appeared to be negligible (4 and 6 msec), so that the onset of both waveforms can be considered as being simultaneous. This is in agreement with other studies (Lingman et al, 1986; Lingman and Maršál, 1986).

The significant difference in end-diastolic flow velocity and minimum vessel diameter between the two methods of synchronization is determined by artificially increased end-diastolic flow velocity and minimum vessel diameter values using the fetal ECG. This is due to the lagtime between the R-top of the fetal ECG and onset of both waveforms (Fig. 3). In other words, the cardiac cycles of the fetal ECG precede the cardiac cycles of the blood flow velocity and pulsatile vessel diameter waveforms (Fig. 3).

It can be concluded that the first derivative method is a satisfactory replacement to the fetal ECG as a means of synchronizing blood flow velocity and pulsatile vessel diameter waveforms in the fetal descending aorta. Its easy applicability offers an attractive alternative to the fetal ECG. It will serve as a useful tool in further comparative studies on pulsatile changes in human fetal aortic flow velocity and vessel diameter waveforms both under physiological and pathophysiological circumstances.

Acknowledgement

We are grateful to Dr. F.K. Lotgering for the lamb preparation.

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Explanatory remarks

For the duration of these studies, a spectrum analyser was not available to display all the information from the blood flow velocity waveform. A sub-study was performed to determine the validity of our data that was obtained using a "mean velocity estimator". The data from this sub-study are presented below.

2.3 A study to compare the mean velocity estimator used in our studies with the instantaneous mean velocity as calculated by a spectrum analyser

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Abstract

Blood flow velocity signals were obtained from the lower thoracic part of the fetal descending aorta in three normal pregnancies of 28, 32 and 37 weeks gestation. The velocity signals were analysed by both a "mean velocity estimator" and a spectrum analyser. The results from both methods of analysis correlated closely and were in good agreement.

Introduction

A spectrum analyser displays all the information from a Doppler signal. It can therefore be argued that any technique where blood flow velocity is quantified or assessed without the use of a spectrum analyser is erroneous and would provide inaccurate data. A spectrum analyser may be considered as the reference method for calculating the results of blood flow velocities analysed by a "mean velocity estimator" with the results of the same blood flow velocities analysed by means of a spectrum analyser.

Materials and Methods

Mean blood flow velocity waveforms were obtained from the lower thoracic level of the fetal descending aorta in three normal pregnancies of 28, 32 and 37 weeks gestation. A linear array real-time and pulsed Doppler ultrasound system, similar to that described by Eik-Nes et al (1980) was used to carry out the measurements. The technique used to obtain the velocity signals was identical to those described in previous studies (Tonge et al, 1984).
When the reflected ultrasound waves produced a satisfactory blood flow velocity signal, as determined by the operator, a command was given whereby the blood flow velocity was recorded over a 5 second period.

Table I. Results of the period time, maximum frequency, minimum frequency, averaged frequency and pulsatility index from the mean velocity estimator and spectrum analyser for the three normal pregnancies.

Patient No. and gest. age	(wks)	Period Time msec S.A.	P	Maximum frequency (KHz) S.A.	P	Minimum frequency (KHz) S.A.	P	Averaged frequency (KHz) S.A.	P	Pulsatility Index S.A.	P
1.	28	426	425	1.22	1.20	0.27	0.26	0.65	0.61	1.96	1.54
	28	382	395	1.36	1.37	0.29	0.26	0.66	0.64	1.62	1.75
	28	418	425	1.23	1.22	0.18	0.10	0.58	0.51	1.81	2.20
	28	412	412	1.16	1.30	0.23	0.16	0.52	0.57	1.79	2.00
2.	32	353	362	1.36	1.46	0.24	0.22	0.70	0.73	1.60	1.70
	32	325	329	1.24	1.29	0.25	0.25	0.59	0.60	1.68	1.72
	37	442	443	0.97	1.11	0.22	0.21	0.58	0.65	1.29	1.39
	37	400	410	1.26	1.27	0.27	0.24	0.71	0.70	1.39	1.49
	37	405	408	0.87	0.97	0.14	0.13	0.50	0.55	1.46	1.54
3.	37	417	420	0.94	1.07	0.15	0.08	0.48	0.53	1.65	1.87
	37	394	400	1.01	0.96	0.21	0.20	0.59	0.57	1.36	1.33
	37	420	427	1.10	1.23	0.12	0.05	0.52	0.54	1.88	2.16
Mean ± 1 SD		399.5 ± 32.8	404.7 ± 31.3	1.14 ± 0.16	1.20 ± 0.15	0.21 ± 0.06	0.18 ± 0.07	0.59 ± 0.08	0.60 ± 0.07	1.62 ± 0.21	1.72 ± 0.29
Difference		+5.0 (±4.3)		+0.06 (± 0.07)		-0.034 (± 0.030)		+0.01 (±0.04)		+0.10 (± 0.20)	

SA = Spectrum Analyser; P = Mean Velocity Estimator.
Each line represents analysis over a 5s period.

(1) Mean velocity estimator:

An explanation of the mean velocity estimator can be found in the thesis of Angelsen (1975). Likewise, Angelsen and Brubakk (1976) give a detailed description of the PEDOF (pulsed Echo Doppler flow velocity meter), which incorporates the "mean velocity estimator". Reflected ultrasound waves were sent through a phase-quadrature detection system which enabled flow direction to be distinguished. The signal was then passed through "sample and hold-circuits" prior to being filtered through low-pass and high-pass filters. The filtered signal was fed into the "mean velocity estimator"; the output of which was proportional to the mean velocity in the sample volume.
Via an AD-converter, an Apple II microcomputer sampled, during the 5 second period, the waveform 1000 times. This was a sampling frequency of 200 Hz. An analysis programme detected the heart cycles and determined the period time, peak mean velocity ($cm\ s^{-1}$), end diastolic velocity ($cm\ s^{-1}$), averaged mean velocity ($cm\ s^{-1}$) and the pulsatility index (Gosling and King, 1975) for each cycle. The velocity values were scaled to frequency values in order to make a direct comparison with the frequency output of the spectrum analyser.

(2) Spectrum analyser:

In order for the same signals to be spectrally analysed, a frequency domain processor, similar to that described by Coghlan and Taylor (1978) was built. The quadrature signals from the PEDOF were fed into the frequency domain processor and the emerging signal was centralised around a carrier frequency of 3 KHz. Forward flow, therefore, had frequencies higher than 3 KHz and backward flow had frequencies lower than 3 KHz. The resulting signal was recorded on a RACAL-STORE 14 magnetic tape recorder and subsequently analysed by a single channel spectrum analyser (Nicolet). The spectrum was analysed by a Digital PDP 11/23 computer.
The analysis programme also calculated the period time together with maximum frequency, minimum frequency, averaged frequency of the instantaneous mean velocity and the pulsatility index for each cardiac cycle. As this computer programme was originally designed for adult cardiac work, an adjustment was made in the programme to cater for the increased heart rate that is present in the human fetus.
The two computer programmes defined the period time in the same way. The onset of the cardiac cycle was interpreted by the beginning of the rising slope.
The two sets of results could therefore be compared.

Results

Table I gives the period time, maximum frequency, minimum frequency, averaged frequency and pulsatility index evaluation for the three pregnancies. A total of 12 suitable measuring periods was taken for comparative analysis.
In the comparison between instantaneous mean velocity calculated by the spectrum analyser and mean velocity estimator, the difference in period time, maximum fre-

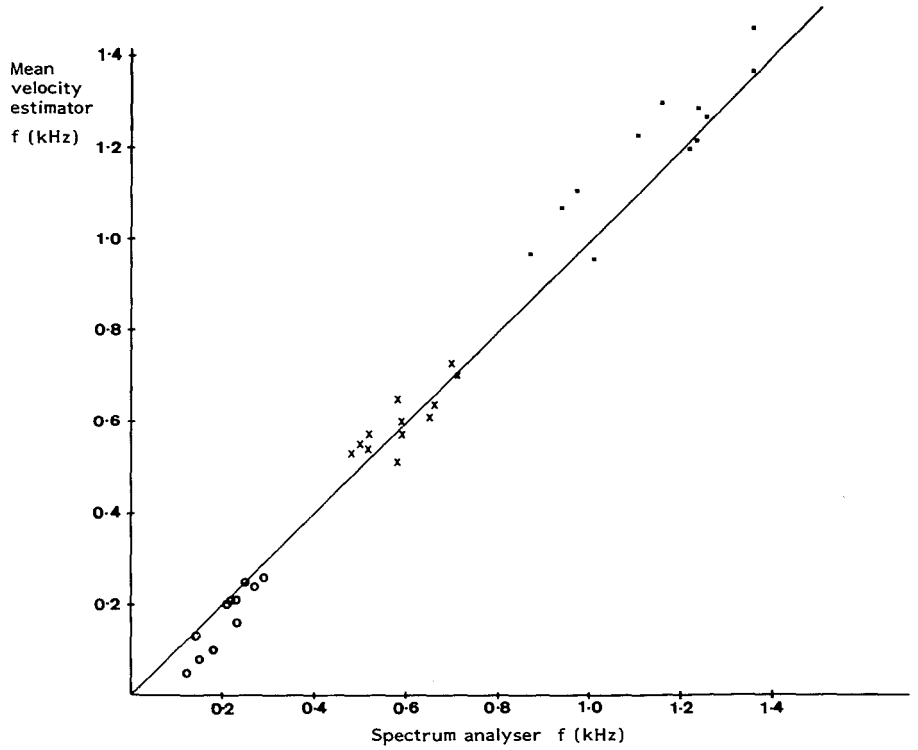

Figure 1. Results of the mean blood flow velocity waveform obtained from the mean velocity estimator plotted against those from the spectrum analyser with reference to the line of identity when x = y. o = minimum frequencies; x = averaged frequencies; ■ = maximum frequencies.

quency, minimum frequency, averaged frequency and pulsatility index was 5 ms + 60 Hz, −34 Hz, +10 Hz and +0.10 respectively.
Figure 1 shows all values plotted around the "line of identity" for maximum, minimum and averaged frequencies.

Discussion

Red blood cells reflect ultrasound waves, that are subject to a change in frequency as a result of the Doppler effect. The change in frequency, or the Doppler shift, can be detected and analysed in several ways. The human ear is, itself, a frequency analyser but its analysis is qualitative not quantitative. Also, red blood cells move within a vessel at different velocities and therefore produce several different frequency shifts within a sample volume. A spectrum analyser can illustrate all the different velocities within the sample volume and arguably should be the most accurate method of interpreting blood flow velocities within a vessel. However, for

the studies on human fetal blood flow in the fetal descending aorta a spectrum analyser was not available. It was important, therefore, to validate our results obtained by a "mean velocity estimator" by performing a short study comparing the results obtained from this apparatus with those obtained from a spectrum analyser.

With the linear array real-time and pulsed Doppler ultrasound complex that was used, the Doppler beam width was 12 mm. As assumptions are made when estimating mean blood flow velocity, namely the cross sectional area of the vessel lumen is completely within the ultrasound beam and uniform scattering is achieved, correct positioning of the sample gate is essential. In the term fetus, the diameter of the descending aorta at the lower thoracic level is approximately 9 mm, so the assumptions were therefore justified. Incorrect positioning of the sample gate would have provided erroneous information as other major vessels, such as the Inferior Vena Cava, would also have been included in the sample volume. An experienced operator would have heard this and also should have been able to readjust the sample gate (Tonge et al, 1984). A spectrum analyser would be able to detect an erroneous signal as it is able to detect directional flow velocities, whereas a mean velocity estimator includes the erroneous data in its waveform. Likewise, a spectrum analyser would display "aliasing" in its negative channel.

In this study, the reflected Doppler shifted ultrasound waves were demodulated and the amplitude and phase of the Doppler-shifted frequencies were detected by phase-quadrature detection systems. It was at this "level" that the mean blood flow velocity signals analysis differed in the two methods.

The phase-quadrature detection system is most commonly used but the output signals are not in a form suitable for directional display by a spectrum analyser (Coghlan and Taylor, 1978).

A frequency domain processor was built to allow separation of the forward and reverse flow velocities. It has the advantage over a phase domain processor as a one channel spectrum analyser can be used to display the direction of flow velocities and the signal can be recorded in a single track of a tape recorder (Coghlan and Taylor, 1978).

The results of this study show that the period time, maximum frequency, minimum frequency and averaged frequency values were in good agreement whether the mean velocity estimator or the spectrum analyser was used. The larger discrepancy in pulsatility index (9%) was due to the small increase in maximum frequency and small decrease in minimum frequency. It is important to point out therefore, that small differences in frequencies that result from the use of different equipment may produce a larger discrepancy in pulsatility indices. This should be considered when interpreting PI values from various centres.

In conclusion, a close correlation between these two methods of analysis exists and results are in close agreement. This finding provides an important basis for our clinical studies.

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Chapter 3

A STUDY ON VOLUME BLOOD FLOW IN THE LOWER THORACIC LEVEL OF THE FETAL DESCENDING AORTA IN NORMAL LATE PREGNANCY

Introductory remarks

The first data on volume blood flow in the fetal descending aorta began to emerge in the late nineteen seventies and early eighties (Eik-Nes et al, 1980a; 1980b). This is comparatively recent and so characteristics of the blood flow waveform have still to be defined, and volume blood flow data are relatively scant. The aim of this study was to define normal blood flow velocity and pulsatile vessel diameter waveforms in the descending aorta in the third trimester of pregnancy, and to investigate any changes in volume blood flow that might occur with advancing gestational age.

3.1 **Vascular dynamics in the descending aorta of the human fetus in normal late pregnancy**

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Published in Early Human Development, vol. 9:21-26 (1983)

Summary

Fetal blood flow velocity and diameter changes in the lower thoracic part of the descending aorta were compared in twenty normal pregnancies between the gestational age of 30 and 41 weeks. The mean blood flow velocity remained constant throughout the study period whereas a significant increase in vessel diameter was observed. The significant increase in aortic stroke volume and blood flow was in correlation with this diameter change.

Key Words: real time ultrasound, pulsed Doppler, fetal blood flow velocity, fetal pulsatile diameter change.

Introduction

Fetal cardiovascular behaviour is an important source of information about fetal well being. Due to the inaccessability of the major fetal vessels, our knowledge of fetal cardiovascular dynamics has been limited to date. The introduction of real-time ultrasound scanners with high quality imaging and time-motion (M-mode) recording systems, however opened the possibility of studying various geometrical and functional aspects of the human fetal and early neonatal heart (Allan et al, 1982; Griffin et al, 1983; Sahn et al, 1980; Wladimiroff and McGhie, 1981a; 1981b; Wladimiroff et al, 1981). Recently, Doppler blood velocity signals have been obtained from the fetal descending aorta and umbilical vein by means of pulsed-wave Doppler systems (Eik-Nes et al, 1980b; Gill and Kossoff, 1979; Griffin et al, 1983) and from the umbilical artery using continuous-wave Doppler ultrasound (Stuart et al, 1980; 1981).
In an effort to collect more quantitative data on the vascular dynamics of the fetal descending aorta, both the change in blood flow velocity and pulsatile vessel diameter and the relationship between these two characteristics with respect to the cardiac cycle were studied.

Subjects and methods

A total of 20 patients with normal singleton pregnancies between 30 and 41 weeks of gestation gave consent to participate in the study. The gestational age had been calculated from a reliable menstrual history and early ultrasonic measurement of fetal crown-rump length or biparietal diameter. Ten patients were between 30 and 35 weeks gestation and 10 patients were between 36 and 41 weeks gestation. Using a combined real-time scanner and pulsed Doppler system as described by Eik-Nes et al (1980a; 1980b), the mean blood flow velocity at the lower thoracic level of the fetal descending aorta was recorded. At the same level, the pulsatile vessel diameter was registered using a dual time distance recorder in a similar way to that described by Gennser and his colleagues (1981).
Due to the interference between the ultrasound signals from the real-time and Doppler transducers, the blood flow velocity and pulsatile vessel diameter could not be measured simultaneously. Instead, these profiles were compared in cardiac cycles of equal R-R intervals as obtained by an external fetal ECG (Fig. 1). For each of these cardiac cycles, the following parameters were established.

- Fetal ECG:
  - beat-to-beat interval for calculations of fetal heart rate (FHR; bpm).
- Mean blood flow velocity profile:
  - peak mean velocity (cm s^{-1});
  - acceleration of mean flow velocity (cm s^{-2}).
- Pulsatile diameter profile:
  - diastolic diameter (mm);
  - maximum diameter change = diameter change at peak height of pulse wave (%);
  - rate of vessel wall expansions (cm s^{-1}).
- Combined flow velocity and pulsatile diameter profile:

- pulsatile flow integrated over one cardiac cycle = aortic stroke volume. During one cardiac cycle the flow velocity and pulsatile diameter profile was divided into 10 equal periods. The blood flow velocity and vessel diameter were sampled at the onset of these periods and the blood flow was subsequently calculated using the formula: $Q = 0.25 \times \Pi \times d^2 \times v$, where Q = flow, d = diameter, and v = velocity. In each patient data analysis took place during 10 cardiac cycles. Comparison of the two patient groups was carried out by Student's *t*-test.

Results

From Figure 1 it can be seen that the blood flow velocity profile is elevated above the baseline throughout the cardiac cycle. There is no dicrotic notch in the pulsatile diameter profile. The actual data are presented as mean values ± SD in Table I.

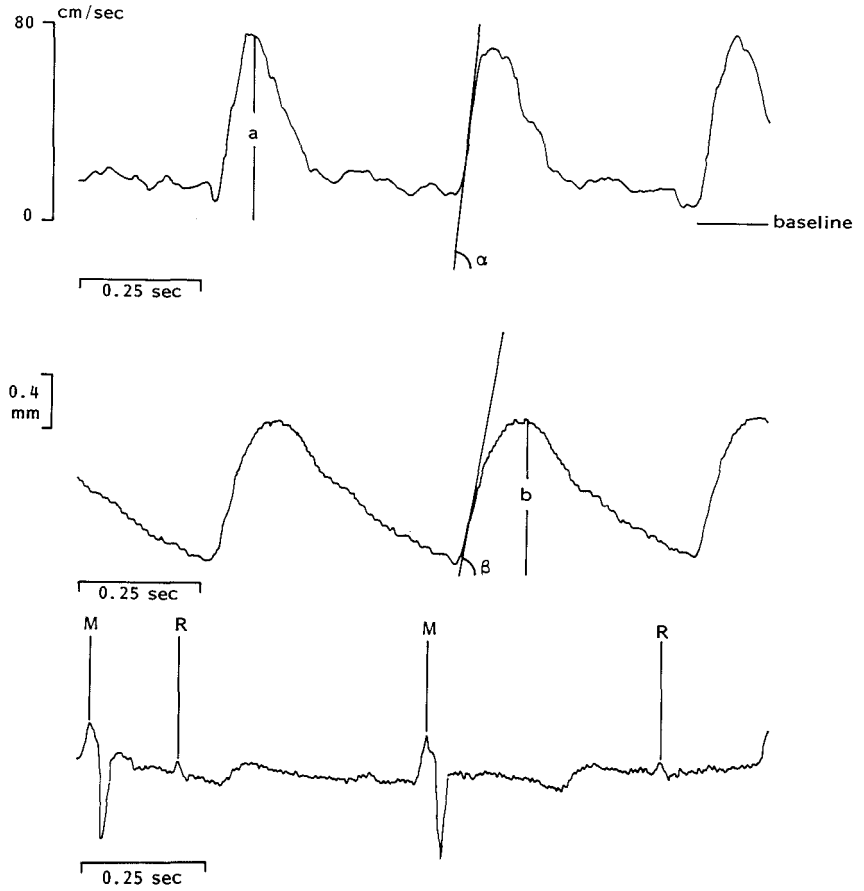

Figure 1. Tracings of mean flow velocity and pulsatile diameter changes compared in cardiac cycles of equal R-R intervals.
a = peak mean velocity (cm s^{-1}); b = diameter change; α = acceleration of mean flow velocity (cm s^{-2}); β = rate of vessel wall expansion (cm s^{-1}); R = R-top fetal ECG; and M = R-top maternal ECG.

Table I. The results of the mean blood flow velocity, pulsatile diameter and combined blood flow velocity and pulsatile diameter profiles (mean ± SD) in the fetal descending aorta.

Gestational age (weeks)	Heart rate (bpm)	Mean blood flow velocity profile		Pulsatile diameter profile			Combined blood flow velocity profile and pulsatile diameter profile	
		Peak mean velocity ($cm\ s^{-1}$)	Acceleration of mean flow ($cm\ s^{-2}$)	Diastolic diameter (mm)	Rate of vessel wall expansion ($cm\ s^{-1}$)	Maximum diameter change (%)	Averaged mean blood flow ($ml\ min^{-1}$)	Stroke volume (ml)
30 - 35	136.7	70.1	1855.9	5.1	1.4	14.6	390.2	2.8
(mean = 31)	± 9.0	± 7.9	± 399.6	± 0.5	± 0.6	± 3.9	± 94.0	± 0.7
36 - 41	142.1	70.4	1748.3	6.5	1.7	12.4	602.0	4.2
(mean = 37)	± 8.9	± 13.3	± 518.2	± 0.9	± 0.5	± 3.2	± 142.0	± 1.2
Statistical significance				$p < 0.0005$			$p < 0.0005$	$p < 0.005$

Fetal heart rate, blood flow velocity profile, rate of vessel wall expansion and maximum diameter change were not significantly different in the two groups. However, the diastolic diameter of the descending aorta, aortic stroke volume and averaged mean blood flow showed a significant increase during the study period.

Discussion

The shape of the blood flow velocity waveform is determined by the interaction of the forward compression wave caused by cardiac systole and reflected waves from the peripheral arteriolar bed (Gosling, 1976; Summer, 1978). The observed elevation of the blood flow velocity profile above the baseline throughout the cardiac cycle reflects continuous perfusion as a result of the low placental resistance. This profile has also been observed by others, both in the human fetus (Eik-Nes et al, 1980b; McCallum, 1981; Stuart et al, 1980) and in the fetal lamb (Dawes, 1968). The absence of a dicrotic notch in the aortic pulse wave may be due to the patent ductus arteriosus, which alters the pressure caused by the aortic valve closure (Sindberg Eriksen et al, 1981). Heart rate, acceleration of mean blood flow velocity, peak mean blood flow velocity and maximum diameter change of the descending aorta demonstrated no change throughout the study period, indicating the presence of a remarkably stable circulatory system in the growing fetus. The constancy of the mean blood flow velocity has been described by other authors (Griffin et al, 1983). The marked rise in aortic stroke volume and averaged mean blood flow during late pregnancy seems to be therefore entirely correlated with the pronounced increase in aortic diameter.

The blood flow figures presented in this paper are higher than those published in a previous paper (Wladimiroff et al, 1981). This is due to the fact that, in the present study, primary Doppler signals were filtered by 150 Hz high-pass filters. This differs from the original investigation in which 600 Hz high-pass filters were used.

In an earlier study (Wladimiroff et al, 1981), a mean left cardiac ventricular stroke volume of 1.4 ml was calculated between 30 and 35 weeks of gestation and one of 2.1 ml betwen 36 and 41 weeks of gestation. Up to now no ultrasonic data on right ventricular stroke volume are available. However, electromagnetic flow studies in the mature fetal lamb suggest that the contribution of the right ventricle to the total cardiac stroke volume is 60% (Anderson et al, 1982) or even 67% (Rudolph and Heymann, 1979), which would result in an estimated total cardiac stroke volume in the human fetus of 3.5 or 4.2 ml in the period between 30 and 35 weeks and of 5.2 or 6.3 ml in the period of 36 to 41 weeks of gestation. Comparison of these estimates of total cardiac stroke volume and the presented aortic volume values shows that the percentage of total cardiac stroke volume directed to the descending aorta varies between 65 and 80%. This is in reasonable agreement with the 70 to 75% found in the fetal lamb (Shinebourne, 1974).

This paper describes a small study of twenty patients, and therefore provides only preliminary data. However, from a clinical point of view, the vascular parameters presented in this paper have already been demonstrated to be of help in establishing fetal cardiovascular conditions during cases of severe fetal cardiac dysrhythmia (Wladimiroff et al, 1983). Further studies in complicated pregnancies should give a picture of the true value of this kind of fetal vascular analysis in the assessment of fetal cardiovascular conditions.

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Chapter 4

A STUDY ON VOLUME BLOOD FLOW IN THE FETAL DESCENDING AORTA IN CASES OF FETAL CARDIAC ARRHYTHMIA

Introductory remarks

Detailed information on cardiac structure and function can now obtained from specialised centres. Echocardiography should be considered as an integral part of the antenatal programme for patients where a fetal cardiac rhythm disturbance is found in the routine antenatal clinic.
In accompaniment to echocardiography, volume blood flow in these patients can provide a sensitive monitor of fetal well-being, particularly on a sequential basis. The following three articles provide information and data on fetal cardiac arrhythmia and structure and volume blood flow.

4.1 Fetal blood flow measurements during fetal cardiac arrhythmia

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Published in Early Human Development, vol. 10:23-34 (1984)

Summary

Three cases of fetal complete heart block, 1 case of fetal bradycardia and 2 cases of fetal supraventricular tachycardia were studied. Using an ultrasonic technique combining real-time ultrasound with a pulsed Doppler system, blood flow measurements at the lower thoracic level of the fetal descending aorta were taken. Despite alterations in rhythm, the blood flow in the aorta descendens was maintained within normal range. With a reduced heart rate, there was an increase in stroke volume, blood flow velocity, acceleration of blood flow velocity and maximum diameter change; conversely, with an increase heart rate the same four parameters were lowered. These alterations reflect changes in cardiac contraction force, and illustrate the ability of the fetal myocardium to maintain blood flow in the growing fetus.

Key words: fetal blood flow, fetal cardiac arrhythmia, real-time ultrasound, pulsed Doppler ultrasound measurements.

Introduction

During the last few years reports on quantitative data on human fetal blood flow have been emerging (Eik-Nes et al, 1980; Maršál et al, 1984; Gill and Kossoff, 1981). Prior to this period information on blood flow had been limited to animal studies due to the inaccessibility of the major fetal blood vessels. Real-time and pulsed Doppler ultrasound provides a non-invasive method of measuring human fetal blood flow. The purpose of this paper is to illustrate the value of this technique in the assessment of fetal haemodynamic changes during fetal cardiac arrhythmia.

Material and methods

Ultrasound studies on fetal cardiovascular structure and dynamics were carried out in 6 pregnant women who were referred for evaluation of fetal cardiac rhythm disturbances between 28 and 36 weeks of gestation. On each of these patients the following examinations were carried out: (1) assessment of fetal size and structure, and amount of amniotic fluid by means of a two-dimensional (2-D) phased array real-time system (Hewlett Packard, 77020A), with particular attention to cardiac structure as well as rate and regularity of cardiac activity; (2) analysis of atrial and ventricular rate and regularity by means of simultaneous time-motion recording of atrial and ventricular activity (Hewlett Packard, 77020 A); (3) recording of fetal ECG from abdominal leads for calculation of fetal heart rate (FHR; bpm); and (4) measurement of mean blood flow velocity and pulsatile vessel diameter changes, during periods of fetal apnoea, at the lower thoracic level of the fetal descending aorta. The methods used were identical to those described in our previous study (Tonge et al, 1983). The same parameters were also established (Tonge et al, 1983). Blood flow in ml kg^{-1} min^{-1} was calculated by assessing fetal weight from ultrasonic measurement of the fetal head and upper abdominal circumferences or by deducing the fetal weight at each gestational age from maternal parity, fetal birth weight and sex according to Kloosterman's tables (Kloosterman, 1970). For each parameter, the mean $\pm$ 1 SD was calculated from 10 consecutive cardiac cycles. The mean value for each parameter was subsequently compared to the normal group. 95% of the normal population is within 2 SD either side of the mean value and 68% of the normal population is within 1 SD either side of the mean. In the presentation of the blood flow results in Tables II and III, any mean value between 68 and 95% was denoted by *; any mean value outside the 95% range was denoted by **.

Results

Table I provides the gestational age at which the first 2-D real time and M-mode examinations were carried out, the type of heart rate disturbance, the clinical data and fetal outcome. The first 3 fetuses (A, B and C) demonstrated complete heart block, which was characterized by atrial contraction rates of approximately 120-140 beats per min (bpm) and independent slow and regular ventricular rates of 48-75 bpm (Fig. 1). Patient A had an emergency caesarean section following a fall in intrapartum fetal blood pH. The infant did well postpartum. Patient B was delivered vaginally at term of a normal-sized infant who subsequently did well.

Table I. The gestational age at first ultrasonic examination, type of arrhythmia, clinical data and fetal outcome.

Patient	Gestational age (wk) at first 2-D real-time and M-mode examination	Heart rate disturbance	Clinical data	Fetal data
A	29	complete heart block	– structurally normal heart – serological evidence of maternal connective tissue disease	term birth (LSCS); ♀; 2550 g; alive and well
B	32	complete heart block	– structurally normal fetal heart – serological evidence of maternal connective tissue disease	term birth (vag.); ♂; 3500 g; alive and well
C	28	complete heart block	– structurally normal fetal heart – right atrial and ventricular dila-dilatation at 36 wk – mother: known case of Waldenström's disease	delivery at 37 wk (LSCS); ♂; 3200 g; died complete absence of A-V node
D	33	bradycardia	– complete A-V septal defect – IUGR	term birth (vag); ♀; 2100 g; so far alive and well; persistent irregular bradycardia due to wandering pacemaker
E	31	supraventricular tachycardia	– structurally normal fetal heart – no response to transplacental digoxin therapy – right atrial and ventricular dilatation at 37 wk	delivery at 37 wk (LSCS); ♀; 2945 g; successful digoxin therapy; alive and well
F	34+	supraventricular tachycardia	– structurally normal heart – no response to transplacental digoxin therapy – right atrial and ventricular dilatation + pericardial effusion at 35+ wk – maternal juvenile onset diabetes mellitus	delivery at 37 wk (LSCS); ♂; 3000 g; successful digoxin therapy

LSCS = Caesarian section IUGR = Intrauterine growth retardation A-V = atrioventricular

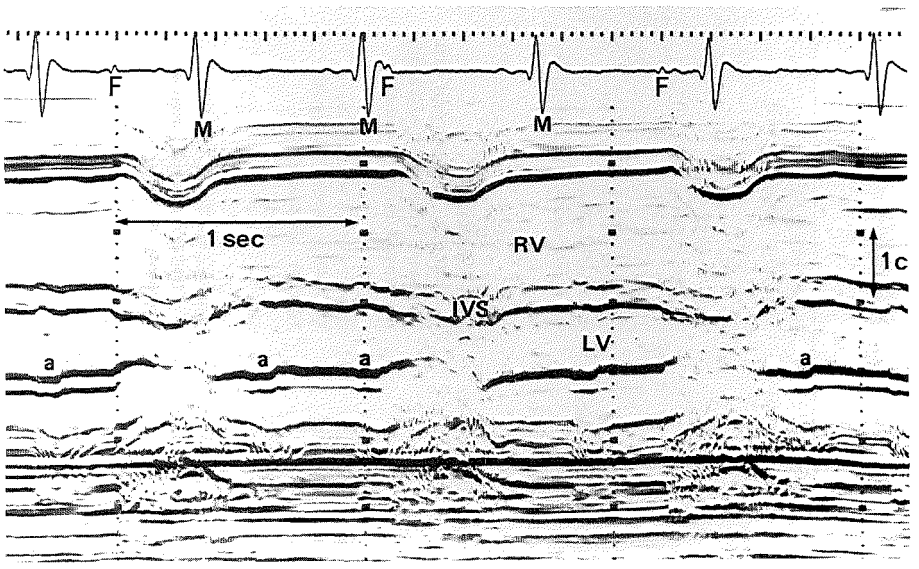

Figure 1. (Stewart et al, 1983). M-mode echocardiogram through the heart of a fetus with complete heart block (Patient A). a = independent atrial contraction on chordae tendinea of the atrial valve; RV = right ventricle; LV = left ventricle; IVS = interventricular septum; M = maternal QRS complex; F = fetal QRS complex.

Neither neonate, so far, has required pacing. The third patient (C) was delivered by caesarean section at 37 weeks following ultrasonic evidence of right atrial and right ventricular dilatation. The infant died 2 days later from congestive cardiac failure. Microscopic examination of the heart showed absence of the atrio-ventricular (A-V) node. Patient D had a bradycardia in association with a severe structural cardiac defect (Table I). The presence of both the bradycardia and structural defects were confirmed post-natally and the rhythm disturbance was found to be due to a wandering pacemaker.

The last two patients (E and F) showed long-term periods of atrial flutter (c. 480 bpm) with 2:1 conduction resulting in a ventricular rate of 231-252 bpm (Fig. 2). Intravenous administration of digoxin to the mothers had no effect on the fetal heart rate patterns. The mothers received 0.75 mg/day. There were no structural cardiac defects. Patient E was deliverd at 37 weeks by caesarean section in view of ultrasonic evidence of right heart dilatation. Neonatally, the tachycardia rapidly responded to digoxin treatment. At 9 months of age the infant had sinus rhythm on a maintenance dose of digoxin. Patient F was prematurely (36 weeks) delivered by caesarean section of a male infant since real-time ultrasound indicated progressive right heart dilatation as well as a pericardial effusion. Postpartum, the heart rate rapidly converted to normal sinus rhythm during digoxin treatment. At 2 months, the infant had sinus rhythm but is still receiving digoxin therapy.

The blood flow data from all 6 patients are shown in Tables II and III, which also include normal blood flow data. These data are extended from our previous study

(Tonge et al, 1983). In the bradycardia group, the mean heart rate varied between 48.1 and 94.4 bpm. Patients A, B and D were characterized by a significant rise in peak mean blood flow velocity, and normal blood flow velocity data were present in patient C. The maximum diameter changes was subject to a moderate or marked increase in patients A and B, and in patient C at 28 weeks. Patient C at 36 weeks and patient D were characterized by an increase in the effective diameter rather than maximum diameter change. As a result a significant rise in aortic stroke volume was observed. Mean blood flow was above 200 ml kg^{-1} min^{-1} in 7 out of 8 examinations. In the tachycardia group, mean heart rate ranged between 230.9 and 252.3 bpm. Peak mean flow velocity was reduced in patient E. The effective vessel diameter measurements were within the normal range, and the maximum diameter changes were decreased, except for patient E at 31 weeks where the effective diameter was elevated and the maximum change was normal. As a result aortic stroke volume was lowered, whereas blood flow per min was normal in patient E and reduced in patient F.

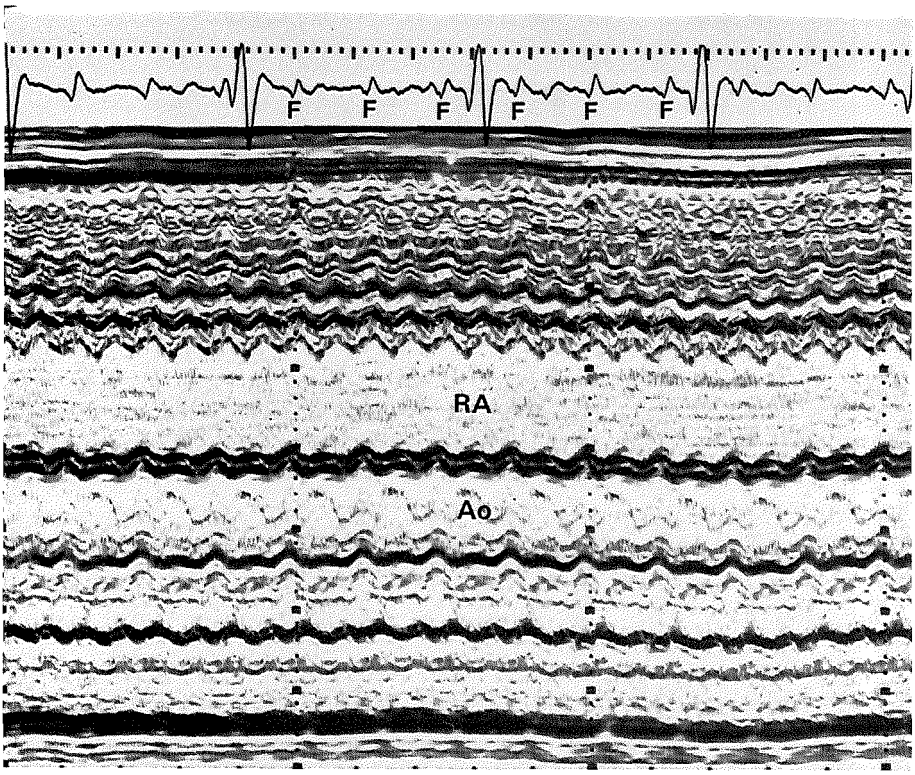

Figure 2. M-mode recording through the right atrium (RA) and aortic root (Ao) of a fetal heart, showing atrial flutter with 2:1 conduction. The QRS complexes of the fetal ECG are depicted on the top of this figure (Patient F).

Table II. The results of mean blood flow velocity, pulsatile diameter and combined blood flow velocity and pulsatile diameter profiles for patients A and B (mean ± SD) in comparison with normal values.

	Gestational age (wk)	Heart rate	Mean blood flow velocity profile	Pulsatile diameter profile		Combined blood flow velocity and pulsatile diameter profile	
	(mean + range)	(bpm)	Peak mean velocity ($cm\ s^{-1}$)	Effective diameter (cm)	Maximum diameter change (%)	Averaged mean blood flow $ml\ min^{-1}$ ($ml\ kg^{-1}\ min^{-1}$)	Stroke volume ml ($ml\ kg^{-1}$)
Normal patients (N = 33)							
9	30 (28-32)	144.1 ± 7.8	70.4 ± 7.3	0.56 ± 0.06	13.9 ± 4.4	392 ± 123 (271 ± 79)	2.7 ± 0.9 (1.9 ± 0.5)
11	35 (33-36)	143.9 ± 13.0	74.6 ± 5.8	0.65 ± 0.07	14.4 ± 2.5	580 ± 124 (266 ± 82)	4.1 ± 1.0 (1.8 ± 0.5)
13	38 (37-40)	141.3 ± 8.2	76.0 ± 11.2	0.7 ± 0.06	12.9 ± 5.0	621 ± 144 (232 ± 78)	4.4 ± 1.1 (1.6 ± 0.6)
Patient A	29	62.2** ± 2.7	76.3 ± 2.8	0.6 ± 0.01	22.3* ± 1.5	333 ± 33 (257)	5.4** ± 0.4 (4.2)**
	33	57.0** ± 0.4	85.3** ± 6.5	0.61 ± 0.01	25.4** ± 2.3	500 ± 86 (250)	8.8** ± 1.5 (4.4)**
	34(+)	57.5** ± 1.9	81.1* ± 2.2	0.64 ± 0.01	28.9** ± 1.5	475 ± 13 (212)	8.2** ± 1.5 (3.6)**
Patient B	32	74.4** ± 2.5	81.5* ± 4.8	0.63* ± 0.01	24.3** ± 1.9	453* ± 27 (247)	6.1* ± 0.7 (3.3)**
	33	69.3** ± 1.7	89.4** ± 1.9	0.65 ± 0.01	20.1** ± 2.4	554 ± 50 (247)	7.3** ± 2.4 (3.3)**

*68-95% of the normal population
**outside 95% of the normal population

Table III. The results of mean blood flow velocity, pulsatile diameter and combined blood flow velocity and pulsatile diameter profiles for patients C, D, E and F (mean ± SD) in comparison with normal values.

	Gestational age (wk)	Heart rate	Mean blood flow velocity profile	Pulsatile diameter profile		Combined blood flow velocity and pulsatile diameter profile	
	(mean + range)	(bpm)	Peak mean velocity ($cm\ s^{-1}$)	Effective diameter (cm)	Maximum diameter change (%)	Averaged mean blood flow $ml\ min^{-1}$ ($ml\ kg^{-1}\ min^{-1}$)	Stroke volume ml ($ml\ kg^{-1}$)
Normal patients (N = 33)							
9	30 (28-32)	144.1 ± 7.8	70.4 ± 7.3	0.56 ± 0.06	13.9 ± 4.4	392 ± 123 (271 ± 79)	2.7 ± 0.9 (1.9 ± 0.5)
11	35 (33-36)	143.9 ± 13.0	74.6 ± 5.8	0.65 ± 0.07	14.4 ± 2.5	580 ± 124 (266 ± 82)	4.1 ± 1.0 (1.8 ± 0.5)
13	38 (37-40)	141.3 ± 8.2	76.0 ± 11.2	0.7 ± 0.06	12.9 ± 5.0	621 ± 144 (232 ± 78)	4.4 ± 1.1 (1.6 ± 0.6)
Patient C	28	52.4** ± 1.8	63.5 ± 6.9	0.58 ± 0.01	31.0** ± 2.5	300 ± 9 (244)	5.7** ± 1.2 (4.6)**
	36	48.1** ± 0.3	68.3** ± 4.7	0.8** ± 0.01	14.9** ± 3.2	391 ± 42 (140)	8.1** ± 0.9 (0.3)**
Patient D	31	94.4** ± 1.2	86.9** ± 2.7	0.64* ± 0.0	16.3 ± 1.2	531 ± 63 (267)	5.8** ± 0.7 (2.9)**
Patient E	31	230.9** ± 6.1	58.4* ± 2.7	0.65* ± 0.0	12.5 ± 0.4	375 ± 47 (299)	1.6* ± 0.2 (1.0)*
	35	231.6** ± 7.2	68.1* ± 4.1	0.68 ± 0.0	5.5* ± 0.4	507 ± 38 (212)	2.2* ± 0.2 (0.9)*
Patient F	34(+)	252.3** ± 14.1	56.2** ± 3.8	0.58 ± 0.0	9.5* ± 1.2	413 ± 34 (154)	1.6** ± 0.2 (0.6)**

*68-95% of the normal population
**outside 95% of the normal population

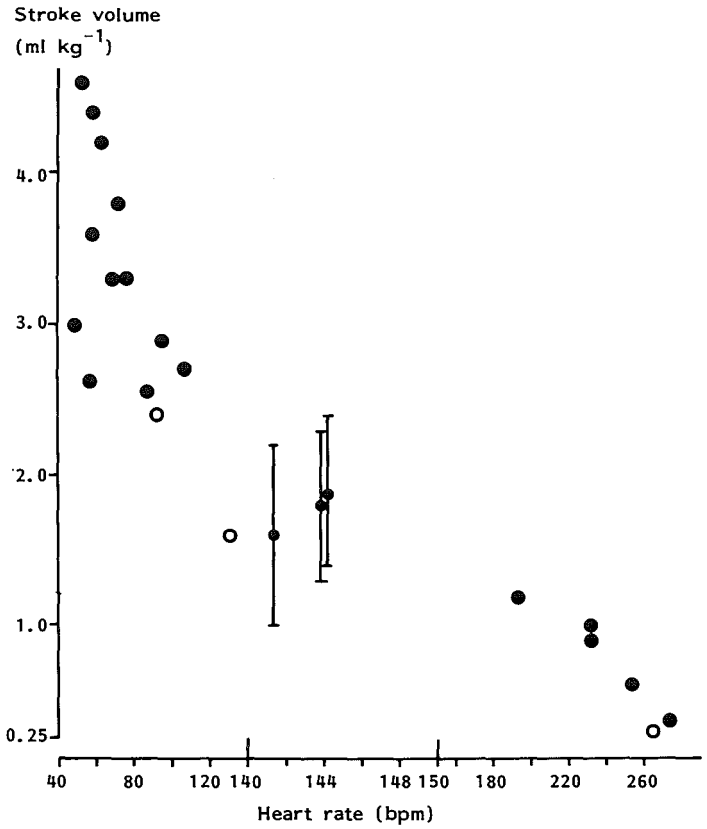

Figure 3. The relationship of aortic stroke volume (ml kg^{-1}) in the lower thoracic level of the fetal descending aorta to heart rate (bpm); ● = arrhythmia cases; ○ = added case (Wladimiroff et al, 1983). Mean values with vertical bars indicating SD.

Figures 3 and 4 represent aortic stroke volume and aortic blood flow per min relative to heart rate for all normal patients and the 6 arrhythmia patients. Also, they include a case of atrial flutter (460-470 bpm) resulting in variable ventricular rates (92, 131 and 264 bpm) at 36 weeks gestation, which is published elsewhere (Wladimiroff et al, 1983). There is a negative correlation between aortic stroke volume and heart rate predominantly in the lower heart rates, whereas blood flow per min in the majority of measurements remains fairly constant.

Discussion

All 6 patients referred for assessment of the fetal cardiac arrhythmia were compared with normal patients from an extended study in our Department (Tonge et al, 1983). Various haemodynamic parameters were contrasted in an attempt to

ascertain any cardiovascular compensatory mechanism that might be present during the arrhythmia.

The patients A, B and C all had fetuses with complete heart block. An association between maternal connective tissue disease, especially systemic lupus erythematosus, and fetal heart block has been described by many authors (McCue et al, 1977; Reid et al, 1978). Patients A and B had serological evidence of connective tissue disease. Both the LE factor and anti-DNA are IgG immunoglobulins and are capable of crossing the placenta (Bridge et al, 1954; Beck et al, 1966). Patient A developed systemic lupus erythematosus clinically 3 months postpartum. Patient C had Waldenström's macroglobulinaemia. Although IgM is the main immunoglobulin that is raised, IgG is often elevated.

Lev et al (1971) described 7 fetal cases of congenital heart block. Four had no A-V node, the other 3 had nodal tissue in the central fibrous body and A-V portion of the pars membranacea. At postmortum fetus C was found to have no A-V node. The pathology found resembled adult cases with cardiac involvement by systemic lupus erythematosus (McCue et al, 1977). In view of the similarity in the fetal and adult pathology, the abnormal immunoglobulins have been suggested as possible pathogenetic factors in congenital heart block (McCue et al, 1977).

An alternative possible pathogenesis of congenital heart block is the failure of connection of the two separate origins of the A-V node and bundle of His.

In fetuses A and B the elevation in peak mean blood flow velocity reflects an increase in cardiac contraction force. Subsequently there is a marked increase in aortic stroke volume and maximum diameter change. By these changes the blood flow in the aorta descendens was maintained. In fetus C, although the fetus was able to maintain blood flow by similar means at 28 weeks, the compensatory mechanisms were unable to cope with the very low heart rate as shown by the reduced blood flow in the descending aorta at 36 weeks' gestation.

It is rare for congenital structural abnormalities to interrupt the conduction pathway. However, in fetus D the complete A-V septal defect was almost certainly the cause of this arrhythmia. The haemodynamic alterations in this fetus mimicked those of the fetuses with complete heart block. An increase in peak mean blood flow velocity and stroke volume was found. The blood flow (ml kg^{-1} min^{-1}) in this fetus also remained normal due to these changes. Fetus D had an elevated effective diameter. It was the increase in this anatomical parameter that resulted in the elevated overall blood flow.

Patients E and F had fetuses with atrial flutter with 2:1 conduction. Supraventricular tachycardia may arise from abnormal automaticity and/or abnormal conduction (Shenker, 1979). Although it tends to be well tolerated in utero (Shenker, 1979; Newburger and Keane, 1979), it can result in cardiac decompensation in the fetus as has been found in our study and in other studies (Silber and Durnin, 1969; Dusemic et al, 1982). The incidence of supraventricular tachycardia with a congenital heart defect is 5 to 10% (Shenker, 1979). Maternal diabetes also increases the risk of congenital heart disease (McCallum, 1981). Patient E had juvenile onset diabetes mellitus. Neither fetus, however, had structural abnormalities in the heart. There was no response to maternal digoxin therapy in either fetus. Digitalis is a recognised method of treatment of fetal supraventricular tachycardia (Newburger and Keane, 1979; Kerenyi et al, 1980), though overall response to

digoxin seems to be variable (Newburger and Keane, 1979). It is important to analyse the exact type of supraventricular tachycardia, either by fetal ECG or M-mode, as a guide to predicting the response to digoxin.

In fetuses E and F the compensatory mechanisms present during the tachycardia were the reverse of those seen during bradycardia, although less pronounced. Figures 3 and 4 suggest that the Frank-Starling mechanism is operational in the human fetal heart, as has been pointed out in our studies (Eik-Nes et al, 1980; Maršál et al, 1984; Wladimiroff et al, 1981; 1983), resulting in the maintenance of blood flow within the normal range. It also shows that this mechanism is particularly effective at the lower heart rates, whereas in the normal range and particularly during tachycardia the fetal heart seems to operate near the plateau of the Starling function curve.

When the heart rate is less than 50 bpm (fetus C at 36 weeks gestation) or more than 250 bpm (fetus F at 34 + weeks gestation, and added case (Wladimiroff et al, 1983), there is a fall off both in aortic stroke volume and blood flow, suggesting that heart

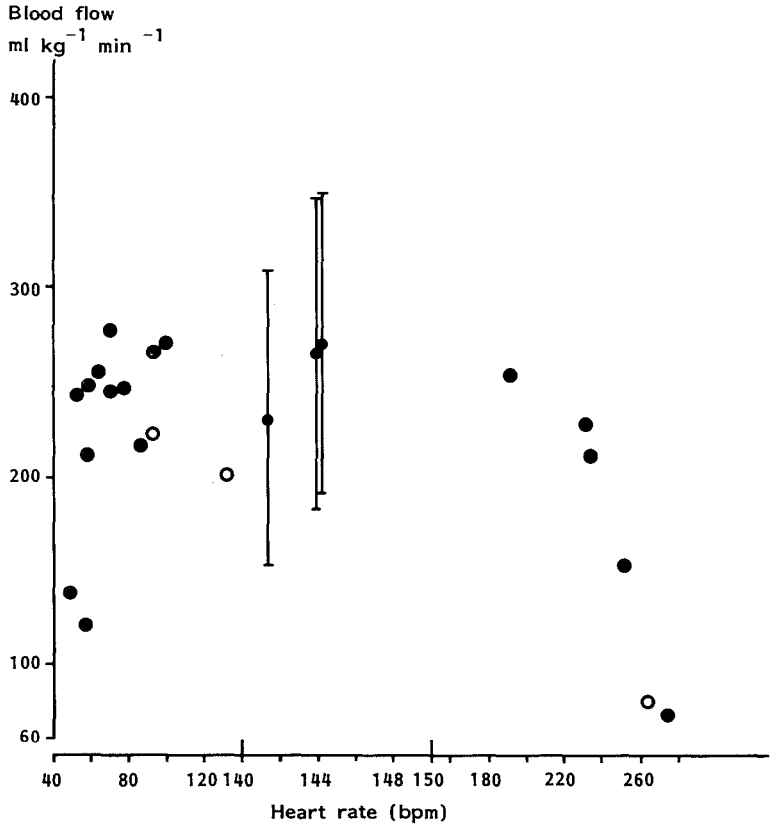

Figure 4. The relationship of blood flow (ml kg^{-1} min^{-1}) in the lower thoracic level of the fetal descending aorta to heart rate (bpm); • = arrhythmia cases; ○ = added case (Wladimiroff et al, 1983). Mean values with vertical bars indicating SD.

rates of around 50 and 250 bpm are the functional limits of the fetal myocardium to the Frank-Starling mechanism. These fetuses all developed intrauterine signs of congestive cardiac failure necessitating delivery. In fetus E, ultrasound signs of early cardiac decompensation were evident. At a persistent heart rate of around 230 bpm the fetus was still able to maintain normal aortic flow despite a suggestion of fall off in aortic stroke volume. It is clear from the results that the fetal circulation is remarkably stable with efficient compensatory mechanisms within a physiological range.

In conclusion, the presence of fetal cardiac rhythm may be indicative of an at-risk fetus. Measurement of fetal blood flow in such cases may give the obstetrician additional information about fetal well-being. In the light of the present findings and with the inevitable improvement in equipment, quantitative evaluation of fetal vascular dynamics should be exploited to the full in future studies.

Acknowledgements

We would like to thank Dr. H. Bal, Dr. H. Kanhai, Mrs. de Klever, Dr. Meerman, Dr. F.H.F. Plantema and Dr. L.A.M. Peeters for referring the patients to our Department.

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4.2 Fetal cardiac arrhythmia and its effect on volume blood flow in the descending aorta of the human fetus

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Published in Journal of Clinical Ultrasound, vol. 14: 607-612 (1986)

Summary

Using a two dimensional linear array real-time and pulsed Doppler ultrasound complex, volume blood flow measurements were made in 86 normal pregnancies, seven cases of fetal bradycardia and seven cases of fetal tachycardia, at the lower thoracic level of the fetal descending aorta. During fetal cardiac arrhythmia, volume blood flow per kg fetal weight was maintained within the normal range, until heart rates reached around 50 bpm and 230 bpm when volume blood flow diminished. The changes observed suggest that the Frank-Starling mechanism is functional in the fetal myocardium and demonstrate the stability of the fetal circulation.

Key words: fetal blood flow, fetal cardiac arrhythmia, real-time ultrasound, pulsed Doppler ultrasound

Introduction

Combined two dimensional real-time and continuous wave or pulsed-wave Doppler ultrasound systems are increasingly being used to record blood flow velocity waveforms in the human fetus. Measurements of volume blood flow in the fetal descending aorta were first described by Eik-Nes et al (1980). Volume blood flow incorporates both flow velocity and vessel size. It is subject to errors, especially when the vessel diameter is measured. Any error in diameter measurement will be squared when the vessel area is calculated (Griffin et al, 1983; Eik-Nes et al, 1984; Tonge et al, 1984a). Volume blood flow measurements should therefore only be carried out when gross volume changes are expected, as has been pointed out by Tonge et al, (1984b) in a preliminary paper on fetal cardiac arrhythmia. The present paper will discuss the value of volume flow measurements in the fetal descending aorta in the clinical assessment of fetal cardiac rhythm disturbances.

Material and Methods

Fourteen pregnant subjects, who were referred for evaluation of a fetal cardiac rhythm disturbance were studied. All subjects were between 26 and 38 weeks of gestation. The following examinations were performed on each patient:

a. assessment of fetal size and structure, and amount of amniotic fluid by either a two-dimensional phased array real-time system (Hewlett-Packard 77020 A) or a

mechanical sector scanner (Diasonics CV 400).
Particular attention was paid to cardiac structure, and the rate and regularity of the cardiac activity;

b. analysis of atrial and ventricular rate and rhythm by means of a simultaneous time-motion recording (Hewlett Packard 7020 4A);
c. recording of fetal ECG from abdominal leads for calculation of the fetal heart rate (FHR; bpm);
d. measurement of mean blood flow velocity and pulsatile vessel diameter changes at the lower thoracic level of the fetal descending aorta.

The system that we used (PEDOF) was introduced by Eik-Nes et al (1980). First the fetal descending aorta was located by means of a two dimensional (2-D) dynamically focused linear array transducer. The sound velocity calibration marks were set at 1540 m s^{-1}. The transducer frequency was 3.5 MHz, and the axial and lateral resolution were 1 and 3 mm, respectively. A 2 MHz pulsed-Doppler transducer with a diameter of 12 mm was used for measurement of the blood velocity. The ultrasound pulses were emitted with a duration of 10 μs each at a repetition frequency of 6.5 or 9.75 KHz, which allows measurement of velocities up to 1.7 m s^{-1} to a depth of 8.5 cm and velocities up to 1 m s^{-1} to depth of 11.0 cm. The Doppler probe was attached to the linear array real-time transducer so that the Doppler beam intersected the fetal descending aorta at a fixed angle of 45°. The beam direction with the sample gate position (electronic marker) could be displayed on the real-time screen. The mean blood flow velocity was measured at the lower thoracic level of the descending aorta. The pulsatile vessel diameter was registered at the same level using a dual-time distance recorder (Gennser et al, 1981). Simultaneous recording of blood flow velocity pulsatile diameter is not possible due to the unacceptable interference between the ultrasound signals from real-time and Doppler transducers. Instead, these profiles were compared in cardiac cycles of equal R-R intervals as obtained by an external fetal ECG (Tonge et al, 1983).

From the mean blood flow velocity and pulsatile diameter profiles, the pulsatile flow integrated over one cardiac cycle (aortic stroke volume) was constructed (Tonge et al, 1983). During one cardiac cycle the flow velocity and pulsatile diameter profiles were divided into 5 ms periods. The blood flow velocity and vessel diameter were sampled at these points and volume flow was subsequently calculated using the formula: $Q = 0.25 \times \pi \times d^2 \times v$, where Q = flow, d = diameter and v = velocity.

Aortic stroke volume in ml kg^{-1} and blood flow in ml kg^{-1} min^{-1} was calculated. For both parameters the mean $\pm$ 1 SD were calculated from 10 cardiac cycles. From patients on whom several flow measurements were performed, only the results of the last measurement will be presented. In one patient, however, widely varying heart rates were observed, resulting in significant changes in aortic blood flow.

The results of the 14 cases of fetal cardiac arrhythmia were compared with those from 86 normal pregnancies – a cross sectional study. Gestational age was calculated from a reliable menstrual history and an early ultrasonic measurement of fetal crown-rump length or biparietal diameter.

Birthweight was estimated either from early ultrasonic measurement of the fetal head and upper abdominal circumference (Eik-Nes et al, 1982) (12 patients) or by deducing the fetal weight at each gestational age from maternal parity, fetal birth

weight, and sex according to Kloosterman's tables (Kloosterman 1970) (88 patients). Normal pregnancies had normal biparietal diameters (BPD), head circumference (HC), and upper abdominal circumference (AC) measurements according to nomograms of Campbell (Campbell, 1976) and a birth weight between the 10th and 90th percentiles according to Kloosterman's tables (Kloosterman, 1970). All patients were non smokers. Ninety-five percent of the normal population were within 2 SD of the mean value, and 68% were within 1 SD of the mean value.

An analysis of variance was performed on all normal results to ascertain the statistical significance of any changes in normal values with increasing gestational age. A regression analysis was performed to determine the relationship among PV, SV, and FHR.

Results

Table I presents the heart rate (FHR; bpm), peak flow velocity (PV; cm s^{-1}), aortic stroke volume (SV; ml and ml kg^{-1}), and volume blood flow (VBF; ml min^{-1} and ml kg^{-1} min^{-1}) at 2-week intervals in 86 normal pregnancies between 26 and 39 weeks of gestation. With increasing gestational age, FHR, PV, SV (ml kg^{-1}) and VBF (ml kg^{-1} min^{-1}) did not change significantly; SV (ml) and VBF (ml min^{-1}), on the other hand, increased with increasing gestational age ($p < 0.001$). Table II presents the same flow parameters, the type of cardiac disturbance, relevant clinical data, and fetal outcome for the 14 patients with fetal cardiac arrhythmia.

The FHR varied between 44.7 and 269 bpm, PV between 24.7 and 84.9 cm s^{-1}, SV between 0.3 and 3.9 ml kg^{-1}, and VBF between 69.3 and 290.3 ml kg^{-1} min^{-1}. Congenital heart block (CHB) was established in six cases and a bradycardia secondary to a wandering pacemaker in one case. In the bradycardia group, there were four cardiac structural defects. Supraventricular tachycardia (SVT) was diagnosed in four cases, one of which was Wolff-Parkinson-White syndrome. (There were three cases of atrial flutter [AF]). In one patient (case N) there were episodes of normo- and bradycardia in aasociation with AF. Further information on this patient has been published elsewhere (Wladimiroff et al, 1983).

Figures 1 and 2 relate FHR (bpm), SV (ml kg^{-1}; fig. 1) and PV (cm s^{-1}, fig. 2). Between 50 bpm and 230 bpm there was a negative correlation between SV and FHR ($R = -0.84$; $R^2 = 0.71$). Below 100 bpm there was a marked rise in SV with maximum values around 50 bpm, but, between 100 bpm and 230 bpm, SV was fairly constant. In the two cases below 50 bpm (A and B) a reduction in SV was observed. On the other hand, in cases I, J, K, H, M and N, when heart rates were around 230 bpm there was also a reduction in SV. The PV data showed a similar pattern although the increase in the lower heart rate change is less marked than for SV ($R = -0.67$; $R^2 = 0.44$). As can be seen from Table III all 8 cases which had evidence of cardiac failure had heart rates either below 50 bpm or above 230 bpm.

Discussion

At present there are three methods of assessing fetal cardiac arrhythmia. Two-dimensional real-time ultrasound provides structural information of the fetal

Table I. Fetal heart rate (FHR), peak flow velocity (PV), volume blood flow (VBF) and aortic stroke volume (SV) values for our normal study group (mean ± SD).

Gestational age (wks)	26-27	28-29	30-31	32-33	34-35	36-37	38-39	P value
No. of patients	7	9	11	16	13	19	11	
FHR (bpm)	143.0 ± 9.3	143.0 ± 6.7	144.9 ± 6.0	139.4 ± 7.4	139.8 ± 4.2	140.3 ± 7.7	139.0 ± 6.1	
PV (cm s^{-1})	72.0 ± 10.0	69.7 ± 7.3	74.7 ± 10.2	74.8 ± 8.2	75.3 ± 7.0	79.3 ± 8.9	78.9 ± 9.0	
VBF (ml min^{-1})	319.4 ± 62.0	340.6 ± 54.2	413.5 ± 96.6	493.0 ± 124.3	570.0 ± 71.3	692.5 ± 185.6	720.3 ± 138.0	$P < 0.0001$
(ml kg^{-1} min^{-1})	286.1 ± 57.2	295.9 ± 57.8	291.6 ± 84.8	266.7 ± 73.7	262.3 ± 76.3	260.0 ± 71.5	235.1 ± 38.3	
Aortic SV (ml)	2.2 ± 0.5	2.4 ± 0.4	2.8 ± 0.7	3.6 ± 0.9	4.1 ± 0.5	5.0 ± 1.5	5.2 ± 0.9	$P < 0.0001$
(ml kg^{-1})	2.0 ± 0.4	2.1 ± 0.4	2.0 ± 0.6	1.9 ± 0.6	1.9 ± 0.5	1.9 ± 0.6	1.7 ± 0.2	

Table II Fetal heart rate (FHR), peak flow velocity (PV), volume blood flow (VBF) and aortic stroke volume (SV) values for our fourteen cases of fetal cardiac arrhythmia (mean ± SD). ** = outside 95% of the normal population; * = 68-95% of the normal population range.

Patient	Gestational age (wks)	FHR (bpm)	PV (cm s^{-1})	VBF		Aortic SV	
				ml min^{-1}	ml kg^{-1} min^{-1}	ml	ml kg^{-1}
BRADYCARDIA GROUP							
A	30	44.7** ± 0.8	42.6** ± 5.1	152.7** ± 30.5	104.6**	3.4 ± 0.7	2.3
B	36	48.1** ± 0.3	68.3* ± 4.7	391.2* ± 42.3	139.7*	8.14* ± 0.9	3.0*
C	34	57.5** ± 1.9	83.0* ± 2.2	474.6* ± 13.3	212.0	5.2** ± 1.4	3.6**
D	34	69.3** ± 1.7	89.4** ± 1.9	553.6 ± 49.7	246.6	7.3** ± 2.4	3.3**
E	37	70.5** ± 1.9	68.9* ± 4.7	378.6** ± 64.2	114.0**	5.7* ± 0.5	1.7
F	33	71.6** ± 1.7	84.0* ± 0.4	575.0 ± 59.5	287.0	7.8** ± 0.7	3.9**
G	33	94.4** ± 1.2	86.9* ± 2.7	530.6 ± 63.4	266.6	5.8** ± 0.7	2.9*
TACHYCARDIA GROUP							
H	33	196.0** ± 7.7	85.2* ± 3.8	495.6 ± 31.6	249.0	2.5* ± 0.2	1.3*
I	35	231.6** ± 7.2	68.1* ± 4.1	507.3 ± 38.1	212.3	2.2** ± 0.2	0.9**
J	34	252.3** ± 14.1	56.2** ± 3.8	413.3** ± 33.9	154.2*	1.6** ± 0.2	0.6**
K	38	269.0** ± 44.1	28.5** ± 2.4	290.3** ± 16.8	96.7**	1.1** ± 0.3	0.4**
L	28	224.6** ± 3.7	52.1** ± 1.7	288.6* ± 7.5	260.0	1.3** ± 0.02	1.2**
M	28	228.2** ± 3.8	36.5* ± 1.3	93.5** ± 3.2	69.3**	0.4** ± 0.0	0.3**
N	36	131.0 ± 3.6	64.0 ± 2.8	587.0 ± 23.0	206.0	4.5 ± 0.2	1.6
		92.0** ± 1.6	73.1 ± 4.9	637.0 ± 76.0	223.5	6.9 ± 0.8	2.4
		264.0** ± 11.0	26.1** ± 1.5	231.0** ± 15	81.1**	0.9** ± 0.1	0.4**

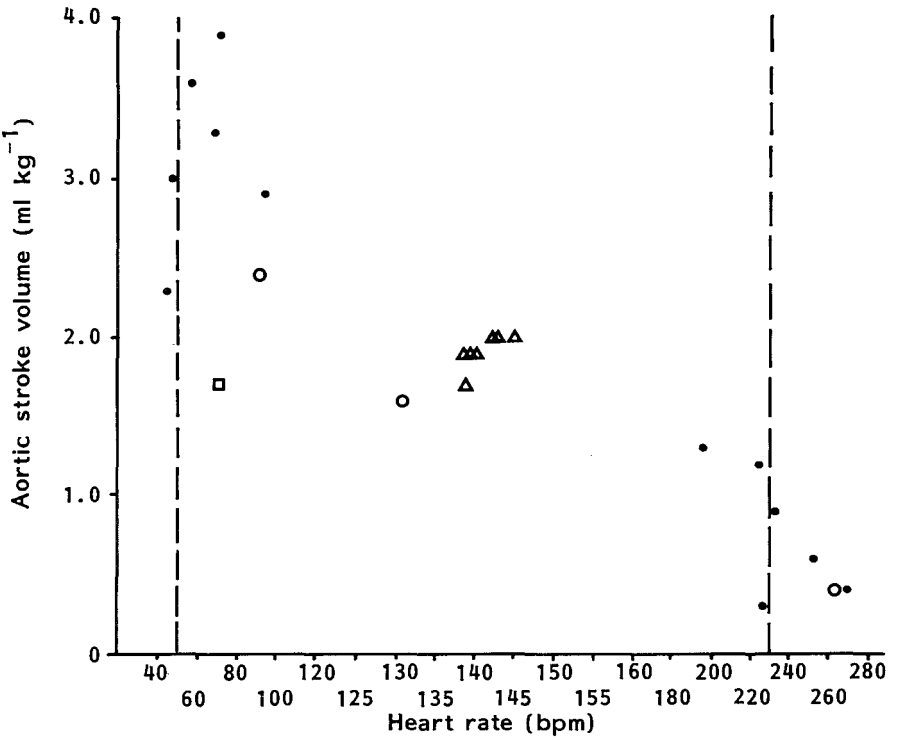

Figure 1. Plot of aortic stroke volume (ml kg^{-1}) against fetal heart rate (bpm). ○ = arrhythmia cases. △ = mean value of our normal study group. □ = case E; ○ = case N. (3 heart rates).

myocardium and also evidence of any fetal cardiac compromise. M-mode studies provide information on the type of arrhythmia and in conjunction with a fetal ECG will demonstrate the electrical activity of the cardiac events. They also provide information on cardiac geometry, in particular the right-to-left ventricular relationship (Wladimiroff et al, 1982).

Thirdly, pulsed Doppler ultrasound in association with real-time ultrasound reflects more directly cardiovascular dynamics. However, volume blood flow (VBF) measurements must be regarded with great caution. Not only are errors inherent in the technique of measurement itself (Griffin et al, 1983; Eik-Nes et al, 1984; Tonge et al, 1984a), but they also arise from the assessment of fetal weight by ultrasound. Only gross changes that occur in VBF measurement, therefore, may be regarded as significant and even then they are only guidelines. Such gross changes however did occur in our study of fourteen cases of fetal cardiac arrhythmia.

In our normal study group, SV and VBF (ml and ml min^{-1}) increased with advancing gestational age. This rise is due to an increase in the actual dimensions of the fetal heart and aorta, and not to any alteration in blood flow velocity (Tonge et al, 1983; Maršál et al, 1984). On the other hand, SV and VBF (ml kg^{-1} and ml kg^{-1} min^{-1}) did not alter significantly, indicating that cardiac output parallels fetal weight with

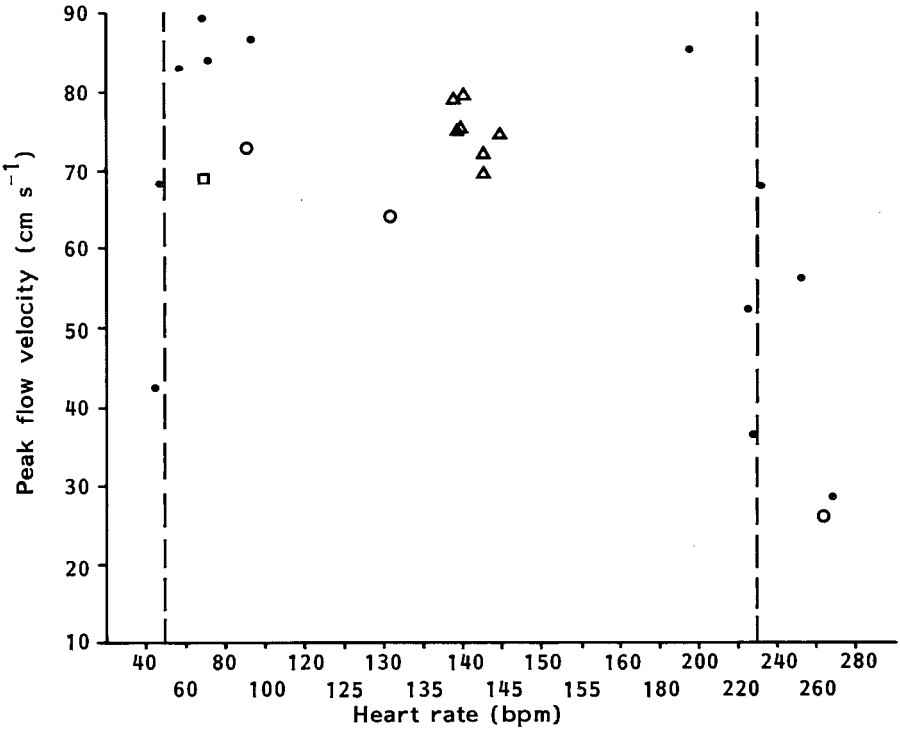

Figure 2. Plot of peak flow velocity (cm s^{-1}) against fetal heart rate (bpm). △ = mean value of our normal study group; ○ = arrhythmia cases; □ = case E.; ○ = case N. (3 heart rates).

advancing gestation. This has also been pointed out by Vosters in his ultrasonic studies of left ventricular cardiac output (Vosters, 1983). In all cases of fetal cardiac arrhythmia VBF (ml min^{-1} and ml kg^{-1} min^{-1}) was maintained within the normal range when heart rates were between 50 bpm and approximately 230 bpm, with the exception of cases C and E. In the normal heart rate range, the changes in cardiac output are mainly determined by heart rate, since here the myocardium is functioning at the plateau of the Frank-Starling mechanism (Gilbert, 1980). At lower heart rate levels there seems to be an inverse relationship between SV and heart rate, indicating that cardiac output is maintained through an increase in SV. These data clearly demonstrate that the Frank-Starling mechanism is operational in the fetal heart as has been suggested by us in an earlier preliminary study (Tonge et al, 1984b). The functional limits of this mechanism appear to be around 50 bpm and 230 bpm because there is a reduction in VBF and aortic SV beyond these ranges although the upper limit is less clearly defined.

Case C. had a VBF value only just below the normal range and the heart rate was approaching 50 bpm. Case E. had a bradycardia in association with a right atrial tumour measuring 1.5 cm by 1.5 cm. This tumour would certainly have reduced venous return (VR) and all the measurements within this case are consistent with a reduced VR.

Table III. Type of rhythm disturbance, cardiac structural information, relevant clinical data and fetal outcome for our 14 cases of fetal cardiac arrhythmia. CHB = complete heart block; LSCS = lower segment caesarean section; SVT = supraventricular tachycardia; AF = atrial flutter; RA = right atrial; RV = right ventricular; CCHD = complex congenital heart disease.

Patient	Rhythm disturbance	Cardiac structural abnormality	Fetal outcome
A	CHB	CCHD	RA + RV dilatation, hydrothorax, ascites, 47 XXY died
B	CHB	Absent A-V node on microscopy, otherwise normal	RA + RV dilatation at 36 weeks. 37 wks: LSCS. ♂ 3200 g; died
C.	CHB	None	Term: LSCS ♀ 2550 g, alive and well
D.	CHB	None	Term: vaginal delivery ♂ 3500 g, alive and well
E.	CHB	Right atrial tumour	Term: vaginal delivery ♀ 3915 g, alive and well
F.	CHB	None	37 weeks: vaginal delivery ♂ 3035 g, alive and well
G.	Bradycardia (wandering pacemaker)	Complete atrioventricular septal defect	Term: vaginal delivery ♀ 2100 g, alive and well
H.	SVT	None	Term: vaginal delivery ♀ 3600 g Rhythm resolved spontaneously; alive and well
I.	SVT	None	RA + RV dilatation at 37 wks; 37 weeks: LSCS ♀ 2945 g, successful postnatal digoxin treatment, alive and well
J.	AF	None	RA + RV dilatation, pericardial effusion at 36 wks; 36 weeks: LSCS ♂ 3000 g, successful postnatal digoxin therapy, alive and well
K.	Wolff-Parkinson-White syndrome	None	RA + RV dilatation, pericardial effusion at 38 wks; 38 weeks: LSCS ♂ 3000 g, successful postnatal digoxin therapy, alive and well
L.	AF	None	Ascites; LSCS: 29 weeks ♀ 1200 g, died
M.	SVT	None	Severe fetal hydrops; 31 weeks: LSCS; ♂ 3500 g, died Evidence of antenatal infection
N.	AF	None	RA + RV dilatation pericardial effusion, ♂ 2850 g, alive and well

From figure 2 it can be seen that PV reflects a similar pattern to SV. The PV changes at lower heart rates, although apparently less marked, are statistically significant, but only just. As PV is an easier and more reproducible parameter to obtain, and in view of the inherent errors present in volume flow measurements, PV may be a more useful parameter to study, but greater patient numbers are needed to substantiate this. Table III (a and b) illustrates that an arrhythmia in association with a lowering or inappropriate PV and SV values is always associated with ultrasonic evidence of cardiac failure. PV, therefore, probably reflects to a major degree the cardiac contraction force. In our department a bradycardia in association with a structural abnormality has been found to be highly sinister (Stewart et al, 1983).

The future value of these ultrasound techniques needs still to be assessed, but there are already indications that they are of value in the monitoring of any antenatal treatment, such as digoxin therapy, that may be given transplacentally (Stewart et al, 1983). By these means a fetus can be monitored antenatally and delivered in optimal condition.

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4.3 Arrhythmia and structural abnormalities of the fetal heart

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Published in British Heart Journal, vol. 50: 550-554 (1983)

Summary

Thirty fetuses with cardiac arrhythmias were referred for ultrasonography. This included cross-sectional and M-mode echocardiography and pulsed Doppler analysis of the fetal heart. Three types of arrhythmia were observed: ectopic beats, tachyarrhythmias and bradycardia. Ectopic beats were associated with cardiac structural abnormalities in two cases, resulting in fetal death in one. Tachycardia was not associated with structural defects, but death from cardiac failure occurred in one patient. Transplacental treatment for tachyarrhythmia was not successful in our experience. In the group with bradycardia four cases had congenital cardiac abnormalities and the mortality rate was 50%. When a fetal arrhythmia has been established, careful structural and rhythm analysis is of vital importance in facilitating prognosis, planning of time and mode of delivery, and monitoring of transplacental treatment where indicated.

Increasing attention is being paid to the prenatal diagnosis of cardiac structural defects by means of real-time cross-sectional scanners (Lange et al, 1980; Sahn et al, 1980; Allan et al, 1981; Stewart et al, 1983) and the value of M-mode recordings in the analysis of cardiac arrhythmias (Kleinman et al, 1982; 1983; Wladimiroff et al, 1981; 1983). This study emphasises the importance of careful structural and rhythm analysis of the fetal heart when a cardiac arrhythmia has been established.

Patients and methods

Between January 1982 and April 1983, 30 patients with fetal cardiac arrhythmias were referred to our ultrasound unit. The gestational age ranged from 21 to 41 weeks (median 31.9 weeks), maternal parity from 1 to 6 (median 2), and maternal age from 20 to 36 years (median 27.4 years). There was no history of congenital heart disease.

After initial detection of fetal heart rate or rhythm disturbance by monoaural stethoscope or continuous Doppler equipment, a detailed ultrasound examination was carried out. This examination included overall assessment of fetal size and structure, placental location, and amount of amniotic fluid, a search for cardiac structural defects and possible signs of cardiac compromise such as pericardial effusion, increase in size of the right heart, and ascites.

For these purposes a phased array or mechanical sector scanner with a 3.5 MHz or 5 MHz transducer was used (Hewlett Packard 77020A Ultrasound Imaging System or Diasonics Cardio Vue 100). M mode analysis (Hewlett Packard 77020 A or Diasonics Cardio Vue 100) of atrial and ventricular rate and rhythm, analysis of the

supra-abdominal fetal electrocardiogram (Corometrics Medical Systems Inc 112 Fetal Monitor), and pulsed Doppler assessment of blood flow in the fetal descending aorta (Eik-Nes et al, 1980), reflecting cardiac contraction force, were performed.

Results

Tables I, II and III give the findings on ultrasound and on clinical examination and the fetal outcome. Three types of arrhythmia were observed: ectopic beats (n = 17); tachycardia (> 180 bpm, n = 5), and bradycardia (< 100 bpm, n = 8). The ectopic beats were usually supraventricular and disappeared before or shortly after birth. In one case ventricular extrasystoles were seen. In two (11.8%) cases an associated cardiac structural abnormality was diagnosed. The remaining pregnancies developed uneventfully and resulted in the delivery of a healthy infant.
Bradycardia was established as complete atrioventricular block in five cases (Fig. 1), as second degree atrioventricular block in one case, was uncertain in one case, and probable mild sinus bradycardia in the remaining patient. In four (50%) patients bradycardia was associated with a structural cardiac anomaly. Tachycardia was assessed as paroxysmal supraventricular tachycardia with spontaneous resolution in the 32nd week of pregnancy in one case, atrial flutter with variable atrioventricular conduction and short bursts of normal sinus rhythm in the remaining case. One patient (case 29) had a normal heart rate as shown on the cardiotocogram but was shown to have atrial flutter with variable atrioventricular conduction on M-mode echocardiography (Fig. 2). In three cases, maternal administration of 0.75 mg digitalis daily failed to cardiovert the tachyarrhythmia.

Table I. Clinical and ultrasound data of fetuses with ectopic beats.

Case no.	Gestational age (wk)	Prenatal findings	Outcome
1-15	23-41	SVE (14 cases), VE (1 case)	Term vaginal delivery, healthy infants
16	34	SVE, severe IUGR, univentricular heart, and coarctation of the aorta	Stillbirth at 34 weeks, cardiac pathology confirmed
17	36	SVE, obstructive foramen ovale, gross right heart dilatation	Term vaginal delivery; SVE after birth; at 6 months had normal heart size and rhythm

SVE = supraventricular ectopics; VE = ventricular ectopics; IUGR = intrauterine growth retardation.

Discussion

Disturbances of cardiac rate and rhythm in the fetus are usually discovered on auscultation during routine prenatal care. The fetal cardiotocogram accurately reflects rate and rhythm in the normal range (120-160 bpm) but may be inaccurate during tachyarrhythmia, as seen in case 29 (Kleinman et al, 1983). The fetal trans-

Table II. Clinical and ultrasound data of fetuses with bradycardia.

Case no.	Gestational age (wk)	Prenatal findings	Outcome
18	21	Gross ascites, hydrothorax, CHB, isomeric atria, absent right AV connection, great arterial connections not clearly identified	Pregnancy terminated at 21 weeks; ascites; hydrothorax, left atrial isomerism, univentricular AV connection (single LV), concordant arterial connections, sub-pulmonary stenosis, asplenia, rocker bottom feet
19	28	Maternal Waldenström hyperglobulinaemia, CHB, structurally normal heart, reduced aortic blood flow at 36 wks	Caesarean section at 37 wk; CHB; died two days after birth; intractable congestive cardiac failure; microscopy showed atrial-axial discontinuity
20	28+	IUGR, irregular bradycardia, complete AVSD	Term vaginal delivery; complete AVSD + wandering pacemaker, alive and well
21	29	CHB, structurally normal heart, maternal collagenosis	Caesarean section at term; CHB; clinically well
22	29	Polyhydramnios, ascites, CHB, PE, isomeric atria, complete AVSD, TOF, gross ventricular hypertrophy	Stillborn at 31 weeks; ascites; left atrial isomerism; univentricular left AV connection with straddling AV value; TOF; right aortic arch with aberrant left subclavian artery; asplenia
23	32	CHB, structurally normal heart, maternal collagenosis	Term vaginal delivery; CHB; clinically well
24	34	Mild sinus bradycardia, structurally normal heart	Term vaginal delivery; normal structure and rhythm of heart
25	35	Polyhydramnios, second degree AV block, VSD, great vessels not visualised	Caesarean section at 38 weeks; second degree AV block; died 12 h after birth, TOF, trisomy 18

CHB = complete heart block; AV = atrioventricular; LV = left ventricle; AVSD = atrioventricular septal defect; PE = pericardial effusion; TOF = tetralogy of Fallot; VSD = ventricular septal defect; IUGR = intrauterine growth retardation.

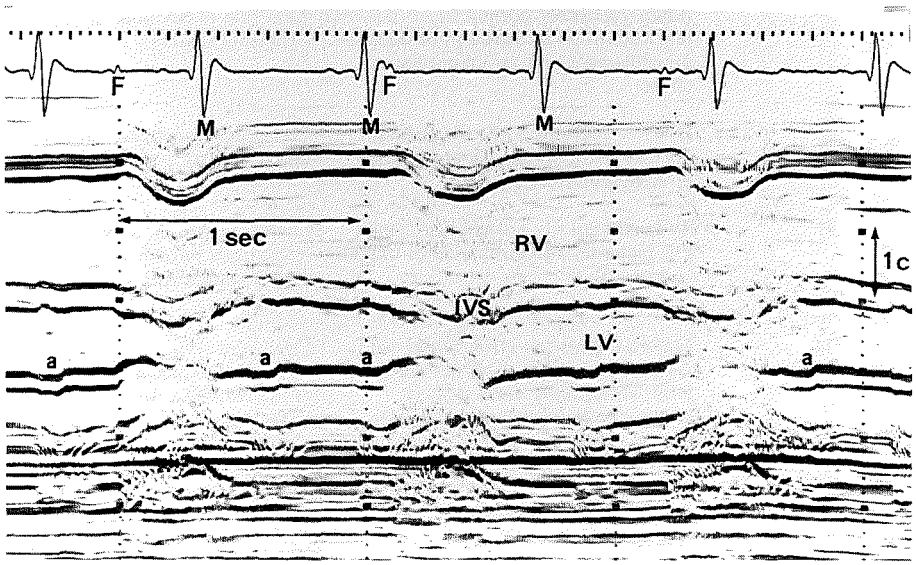

Figure 1. M-mode echocardiogram from case 21 showing complete congenital heart block. F = fetal QRS complex; M = maternal QRS complex; RV = right ventricle; IVS = interventricular septum; LV = left ventricle; a reflects independent atrial contraction on chordae tendinae of mitral valve.

abdominal electrocardiogram monitors ventricular depolarisation but not usually atrial depolarisation and therefore has a limited function in the accurate determination of fetal arrhythmia. Combined cross sectional and M-mode echocardiography provided the most useful means of diagnosing abnormalities of cardiac rhythm and function in isolation, or in combination with structural heart disease. Pulsed Doppler assessment of blood flow in the descending aorta provides additional information on cardiac function since it is well correlated with total cardiac output (Tonge et al, 1983).

In a prospective study of fetal heart rate and rhythm, Southall et al (1980) found an incidence of 1.2% of premature beats, which was similar to that (0.8%) in healthy neonates (Southall et al, 1981). These ectopic beats were considered to be benign and associated with a good prognosis. In our series, however, two (11.8%) cases with ectopic beats had associated structural abnormalities (Fig. 3) resulting in fetal death in one. These instances emphasise the need for detailed structural analysis of the heart in the presence of arrhythmias. Regular screening of a sustained arrhythmia may occur from one of these ectopic beats (Gillette et al, 1976). Vaginal delivery should be possible in cases in which isolated ectopic beats are found.

In our study, bradycardia was associated with a 50% mortality rate. One fetus (case

Table III. Clinical and ultrasound data of fetuses with tachycardia.

Case No	Gestational age (wk)	Antenatal findings	Outcome
26	25	Polyhydramnios; fetal hydrops; atrial flutter with predominantly 2:1 conduction; structurally normal heart; maternal intravenous administration of digitalis, procainamide and verapamil had no effect	Stillbirth at 26 weeks; fetal hydrops; structurally normal heart; block dissection of SA node showed no clear abnormality
27	26	PSVT + multiple SVE; structurally normal heart; spontaneous resolution of arrhythmia at 32 weeks	Term vaginal delivery; structurally normal heart
28	31	SVT; structurally normal heart; mild PE; maternal administration of digitalis had no effect	Caesarean section at 36 weeks; structurally normal heart; control of arrhythmia with digitalis; alive and well at 1 year
29	34	Maternal diabetes; atrial flutter with variable conduction and periods of NSR; structurally normal heart; maternal administration of digitalis had no effect	Caesarean section at 38 weeks; structurally normal heart; control of arrhythmia with digitalis
30	36	Atrial flutter with variable AV conduction; mild PE; structurally normal heart	Caesarean section at 36 weeks; structurally normal heart; control of dysrhythmia with digitalis; alive and well at 1 year

PSVT = paroxysmal supraventricular tachycardia; SVE = supraventricular ectopics; SA = sinoatrial node; PE = pericardial effusion; NSR = normal sinus rhythm; AV = atrioventricular; SVT = supraventricular tachycardia.

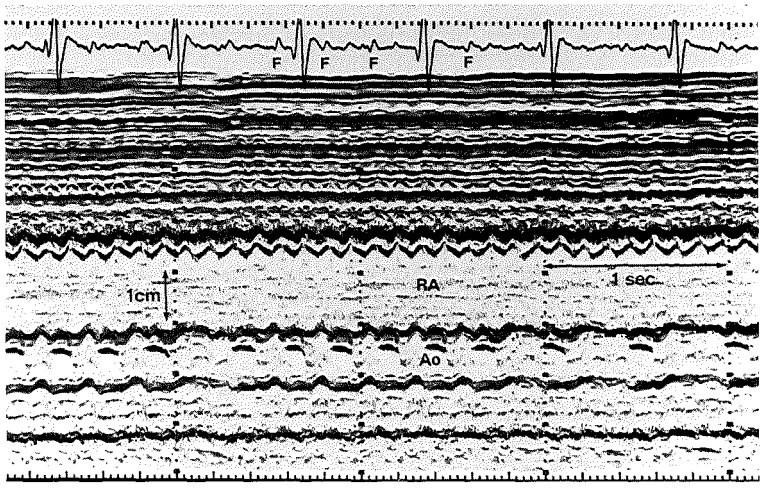

Figure 2. M-mode echocardiogram from case 29 showing atrial flutter with variable atrioventricular contraction as reflected by irregular opening of the aortic (Ao) valve. F = fetal QRS complex; RA = right atrium.

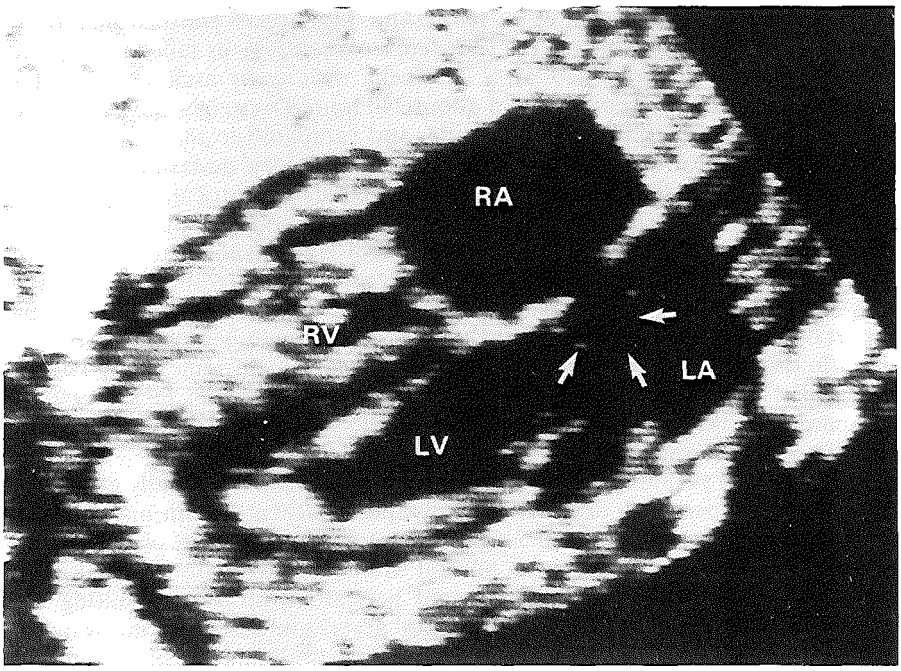

Figure 3. Four chamber view from case 17 showing obstructive structure (arrows) at level of foramen ovale. In real time images the right atrium (RA) and right ventricle (RV) were grossly dilated and the interventricular septum moved paradoxically. LA = left atrium; LV = left ventricle.

19) with no structural abnormality and complete congenital heart block associated with maternal Waldenström's disease died two days postpartum from intractable cardiac failure. The remaining three fetuses had associated structural heart disease and congestive cardiac failure and died in utero or shortly after birth.

It is clear from these data that fetuses with structural heart disease or evidence of congestive cardiac failure in the presence of sustained arrhythmia, or both, have a more ominous prognosis. Until recently Caesarean section has been the method of delivery in cases of fetal congenital heart block without cardiac compromise. Although vaginal delivery was successful in case 23, an emergency Caesarean section had to be carried out in case 21 as fetal scalp pH dropped to 7.07, whereas baseline atrial heart rate remained at 150 bpm without appreciable changes relative to uterine contractions. Furthermore, elective Caesarean section allows optimal timing of the delivery with respect to immediate postpartum care by the neonatologist and paediatric cardiologist. Termination of pregnancy may be recommended (case 18) in cases in which complex congenital heart disease, cardiac failure, and arrhythmia are diagnosed early in pregnancy.

The previable fetus with severe congestive cardiac failure due to tachyarrhythmia presents a serious therapeutic problem, and fetal death may occur in such cases. There have been several reports of successful fetal cardioversion by administration of various drugs to the mother (Lingman et al, 1980; Kerenyi et al, 1980; Harrigan et

al, 1981; Dumesic et al, 1982), digitalis being the mostly commonly used as it readily crosses the placenta (Rogers et al, 1972). Our experiences contrast directly with those of the above authors, as the four fetuses treated by us failed to respond to treatment. Case 26 presented at > 25 weeks with gross ascites and maternal polyhydramnios and a heart rate of about 240 bpm. Over eight days intravenous administration of digitalis, procainamide, and verapamil to the mother failed to convert the tachycardia, and the fetus died at > 26 weeks' gestation. The digitalis dosage was 0.75 mg/day for five days; on the sixth day 1 g procainamide was given over one hour with a maintenance dose of 4 g daily and digitalis was reduced to 0.5 mg; and on the eighth day 10 mg verapamil given over one hour was added because of the worsening fetal condition. The degree of polyhydramnios and ascites may have played some part in the availability of these drugs to the fetus, but a report by Klein et al (1979) describing failure of treatment before the development of hydrops may indicate a more complicated mechanism in some cases. The transmission of verapamil across the placenta is variable (Strigl et al, 1980), but verapamil was selected in this case in which the arrhythmia proved refractory to digitalis and procainamide.

Case 29 showed periods of normal sinus rhythm, which were initially attributed to successful treatment with digitalis. We subsequently learnt that the maternal serum digitalis concentrations were 0.5 ng/ml at the first recording of normal sinus rhythm. Despite the periods of normal sinus rhythm, this fetus developed enlargement of the right heart and mild pericardial effusion, resulting in the delivery by Caesarean section at > 38 weeks' gestation. Careful monitoring by all methods is mandatory in all fetuses with tachyarrhythmia as this is a high risk group. Transplacental treatment must be attempted in the hope of achieving cardioversion and preventing congestive cardiac failure in the previable fetus. In the viable fetus refractory arrhythmias should be further treated by elective Caesarean section and pharmacological or electrical cardioversion immediately after birth.

Acknowledgements

We thank all our colleagues for referring their patients to this ultrasound unit. We particularly thank Professor A.E. Becker (University of Amsterdam) and Dr. E. Essed (Erasmus University, Rotterdam) for their pathology findings. We also thank Hewlett-Packard for donating a 77020A ultrasound imaging system for part of this work, and the Department of Clinical Genetics, Erasmus University, Rotterdam, for providing a Diasonics Cardiovue 100 for our fetal structural abnormality screening programme.

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Chapter 5

A STUDY ON FETAL BLOOD FLOW VELOCITY WAVEFORMS IN CASES OF INTRAUTERINE GROWTH RETARDATION

Introductory remarks

The articles presented in this chapter describe characteristic changes which occur in the blood flow velocity waveforms not only in the descending aorta of the human fetus, but also in the internal carotid and umbilical arteries. They provide an incomplete "map" of velocity alterations in the compromised fetuses, and also illustrate the value of blood flow velocity investigations for the elucidation of the origins of intrauterine growth retardation.

5.1 Blood flow velocity waveforms in the descending aorta of the human fetus in the third trimester of pregnancy: comparison between normal and growth retarded fetuses

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Published in Obstetrics & Gynecology, vol. 67: 851-855 (1986)

Summary

A linear array real time transducer was combined with a pulsed Doppler transducer in order to study and compare the mean blood flow velocity waveform in 77 normal pregnancies and 12 cases of intrauterine growth retardation. All pregnancies were in the third trimester.
In normal pregnancies the peak velocity, end diastolic velocity and pulsatile index remained unchanged with increasing gestational age. End diastolic velocity was lowered or at zero level (high pass filter level) and the pulsatile index was elevated in most cases of severe intrauterine growth retardation. Peak velocity related closely with the quality of the heart rate patterns and the condition of the infant at birth.

Key words: fetal blood flow, blood flow velocity waveforms, real time ultrasound, Doppler ultrasound, intrauterine growth retardation

Introduction

Early diagnosis of intrauterine growth retardation (IUGR) is important to ensure optimal obstetric monitoring and delivery.
Current methods of diagnosing and assessing IUGR include clinical evaluation and various ultrasonic parameters. The latter play an important and widespread role in current obstetric practice, in particular head circumference (HC) and upper abdominal circumference (AC) measurements (Campbell and Thoms, 1977).
With the introduction of real time and Doppler ultrasound systems, a non-invasive method of measuring human fetal blood flow has become available (Eik-Nes et al, 1980; 1984; Griffin et al, 1983; Tonge et al, 1983). However, errors that arise in assessing vessel diameter and fetal weight by ultrasound have resulted in attention turning to qualitative interpretation of blood flow velocity waveforms as a possible method of predicting and diagnosing IUGR. The aim of this study was to compare blood flow velocity waveforms at the lower thoracic level of the fetal descending aorta in normal and growth retarded fetuses.

Material and Methods

Using a combination of linear array real time and pulsed Doppler ultrasound, in a complex similar to that first described by Eik-Nes et al (1980), blood flow velocity measurements were carried out at the lower thoracic level of the fetal descending aorta in 77 normal pregnancies and in 12 cases of IUGR. The techniques used were identical to those described by the authors in previous studies (Tonge et al, 1983). The fetal descending aorta was located using a two-dimensional (2-D) dynamically focused linear array transducer (3.5 MHz). The real time image enabled keeping the aorta parallel to the transducer at all times. The pulsed Doppler transducer (2 MHz) was fixed to the linear array transducer at an angle of 45°, thereby ensuring that the angle of insonation by the Doppler beam to the direction of velocity of the erythrocytes was also 45°. The mean blood flow velocity waveform was recorded over a 5 second period that included at least 10 consecutive cardiac cycles. Ten optimal cardiac cycles were selected and the mean value for the peak velocity (PV), end diastolic velocity (EDV) and pulsatile index (PI) were calculated (Fig. 1) for these cardiac cycles by a microcomputer (Apple II). The pulsatile index used was that first described by Gosling and King (1975) (Fig. 1).
Gestational age varied from 26 to 41 weeks. All measurements were performed in a semirecumbent position and during periods of fetal apnoea, since high amplitude fetal breathing modulates blood flow (Maršál et al, 1984). Normal pregnancies were defined by normal biparietal diameters (BPD), head circumference (HC) and upper abdominal circumference (AC) measurements according to normograms by Campbell (1976), and a birthweight between the 10th and 90th percentiles for gestational age according to Kloosterman's Tables (Kloosterman, 1970) corrected for maternal parity and fetal sex. All patients were non-smokers.
IUGR was defined by:

a. a clinical discrepancy of more than two weeks on fundal height on two successive antenatal appointments combined with ultrasonic findings of upper AC measurements below the 10th percentile in association with normal or reduced HC measurements.

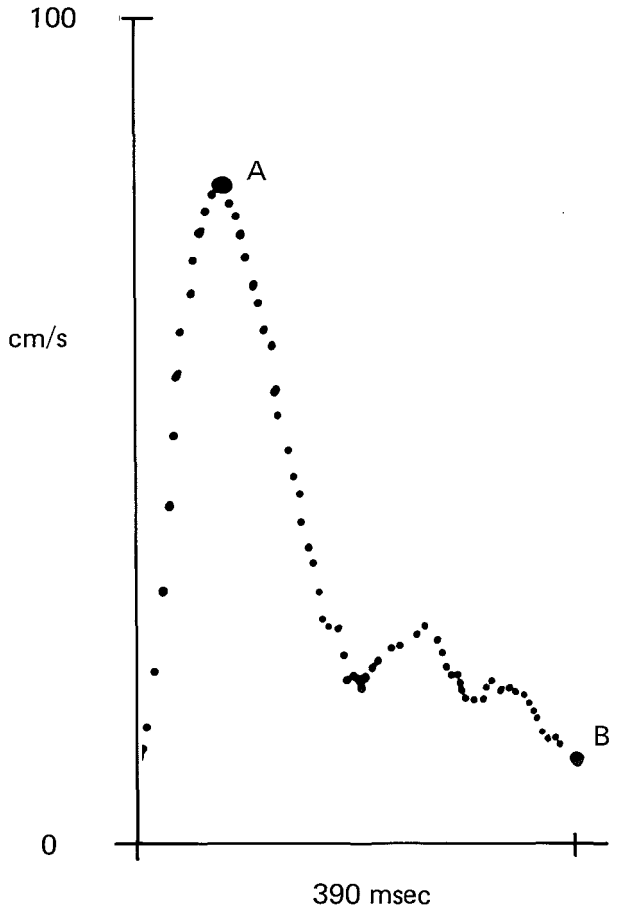

Figure 1. Computer print out of the normal blood flow velocity waveform for one cardiac cycle. Each point represents four sampling points. A = peak velocity (cm s^{-1}); B = end diastolic velocity (cm s^{-1}); PI = A-B/average blood flow velocity.

b. postnatal confirmation by a birthweight below the 10th percentile for gestational age according to Kloosterman's Table (Kloosterman, 1970) corrected for maternal parity and fetal sex. The normal study group was divided into 6 study periods (Table 1) and for each study period the mean ± S.D. of the 3 parameters were calculated. The PV, EDV and PI of the IUGR group were compared with the normal study group. In the presentation of these results any value that was between 68% to 95% of the normal range was denoted by *, and any value outside 95% range was denoted by **.

A normal heart rate pattern was defined as a heart rate pattern with a baseline varying between 110-160 bpm with good beat-to-beat variability, periodic accelerations and no decelerations. An abnormal heart rate pattern was one that deviated from this normal definition.

Table I. Peak Mean Velocity, End Diastolic Velocity, and Pulsatile Index values for our normal study group.

Gestational age (wk)	26 - 29	30 - 31	32 - 33	34 - 35	36 - 37	38 - 41
Mean	28	30^{+3}	32^{+6}	34^{+3}	36^{+4}	38^{+2})
No. of patients	10	10	15	13	16	13
Peak velocity (cm s^{-1})	75.8 ± 9.4	78.5 ± 9.6	74.4 ± 5.7	74.3 ± 6.7	79.4 ± 8.2	77.7 ± 6.2
End diastolic velocity (cm s^{-1})	9.2 ± 3.5	7.4 ± 2.6	8.9 ± 3.2	8.7 ± 2.8	9.4 ± 3.3	9.6 ± 2.7
Pulsatile index	2.0 ± 0.2	2.2 ± 0.3	2.2 ± 0.3	2.2 ± 0.2	2.2 ± 0.3	2.3 ± 0.2

Results

Table 1 provides the mean ± S.D. for PV, EDV and PI with increasing gestational age for our normal study group. PV, EDV and PI did not alter with increasing gestational age.

Table II provides the gestational age at which the first blood flow velocity recording was taken, clinical data and fetal outcome with Apgar scores for the cases of IUGR.

Table II. Gestational age at first mean blood flow velocity recording, clinical data and fetal outcome in 12 cases of intrauterine growth retardation. IUGR = intrauterine growth retardation; PIH = pregnancy induced hypertension; LSCS = Caesarean section; NND = neonatal death; IUD = intrauterine death.

Patient	Gestational age (wks) at 1st recording	Clinical data	Fetal outcome
1	28	1. Symmetrical IUGR 2. PIH	33 wks: LSCS ♂ 1250 g (P5-P10) Apgar score: 9 at 1 min./10 at 5 min.
2	31	1. Asymmetrical IUGR	38 wks: induction ♂ 2010 g (P2.3) Apgar score: 9 at 1 min./10 at 5 min.
3	38	1. Asymmetrical IUGR 2. PIH	38 wks: induction ♂ 1965 g (P < 2.3) Apgar score: 8 at 1 min./9 at 5 min.
4	30	1. Asymmetrical IUGR	39 wks: LSCS ♀ 1500 g (P < 2.3) Apgar score: 9 at 1 min./10 at 5 min.
5	32	1. Asymmetrical IUGR 2. PIH	35 wks: LSCS ♂ 1250 g (P < 2.3) Apgar score: 8 at 1 min./9 at 5 min.
6	31	1. Asymmetrical IUGR	34 wks: spontaneous delivery ♀ 1490 g (P5-P10) Apgarscore: 9 at 1 min./10 at 5 min.
7	28	1. Asymmetrical IUGR 2. PIH (Fulminant)	32 wks: IUD ♂ 770 g (P2.3-P5)
8	27	1. Asymmetrical IUGR 2. PIH 3. positive IgM for cytomegalovirus (results after birth)	32 wks: LSCS ♀ 530 g (P < 2.3) NND
9	35	1. Symmetrical IUGR	35^{+2} wks: IUD Trisomy 13
10	34	1. Asymmetrical IUGR	34 wks: LSCS ♂ 800 g (P < 2.3) Apgar score: 4 at 1 min./8 at 5 min.
11	33	1. Asymmetrical IUGR 2. Essential Hypertension 3. Smoker+++	33 wks: LSCS ♂ 860 g (P < 2.3) Apgar score: 7 at 1 min./9 at 5 min
12	30	1. Asymmetrical IUGR	33 wks: LSCS ♀ 1420 g (P5-P10) Apgar score: 8 at 1 min./10 at 5 min.

Table III. Gestational age, peak mean velocity (PV), end diastolic velocity (EDV), and pulsatile index (PI) value range together with CTG quality in the growth retardation group.

Patient	Gestational age (wks)	No. of measurements	PV	EDV	PI	Heart Rate Pattern
1	28-31	3	75.9 - 80.7	6.3 - 11.6*	1.9 - 2.0	N
2	31-35	4	62.2* - 59.8*	0.0** - 0.53**	2.6* - 3.8**	N
3	38	1	66.3*	0.0**	4.2**	N
4	30-38	7	53.3** - 72.6**	0.0** - 1.7**	2.7** - 4.1**	N
5	32-33	2	63.6** - 75.0	0.0**	3.2** - 3.3**	N
6	31	1	51.8**	0.7**	2.2	N
7	28	1	54.0**	0.0**	3.0**	N
8	29-31	2	43.5** - 44.2**	0.0**	3.2** - 3.4**	ABN
9	$35\text{-}35^{+2}$	2	33.3**	0.0**	2.8** - 3.0**	ABN
10	34	1	35.6**	0.0**	3.4**	ABN
11	33	1	75.9	0.0**	3.9**	ABN
12	30-33	3	54.1** - 69.8	0.0** - 1.3**	2.5 - 3.3**	ABN

N = normal; ABN = abnormal; * = Value between 68% to 95% of the normal range; ** Value outside the 95% range.

Table III provides the range of PV, EDV and PI for 12 cases of IUGR, the number of measurements and the quality of the heart rate pattern on the day of the blood flow velocity recordings. The heart rate patterns were normal in all cases at the time of examination except for cases 8, 10 and 11, and became abnormal within 12 to 48 hours of examination in cases 9 and 12.

Discussion

Several reports have provided quantitative information on human fetal blood flow in the aorta descendens (Griffin et al, 1983; Tonge et al, 1983, 1984; Maršál et al, 1984). All research groups showed that the increase in blood flow that was found with increasing gestational age was due to an increase in cardiac ventricular and aortic dimensions rather than changes in the blood flow velocity. Quantitative measurements of human fetal blood flow must be regarded with great caution, however. Errors that arise in calculating vessel diameters will be squared when the area is calculated. Uncertainty as to where ultrasound waves are reflected from (for example, the muscle layer of the vessel wall or the connective tissue surrounding the vessel) implies that there are inherent errors in diameter measurements. A second source of error is the assessment of fetal weight by ultrasound. For these reasons attention has turned to qualitative interpretation of blood flow measurement of the human fetus, studying variations in blood flow velocity waveforms from the normal patterns that occur in the presence of pregnancy pathology.

The blood flow velocity waveform is formed from several interacting components – the forward compression wave caused by cardiac systole, downstream peripheral resistance, blood viscosity, vascular compliance and the level at which the waveform is recorded (Gosling, 1976; McDonald, 1974; Summer, 1978). The normal waveform is always positive because of the low peripheral resistance circulation that is present in the fetus (Dawes, 1968; McCallum et al, 1978; Stuart et al, 1980; Eik-Nes et al, 1984). The normal waveform (Fig. 1) can be subdivided into systolic and diastolic components which are separated by a notch that coincides with aortic and pulmonary valve closures (Griffin et al, 1984). The systolic moiety reflects the compression wave with the PV value probably being an indicator of cardiac contraction force. The PV does not alter with increasing gestational age. The diastolic moiety and especially the EDV, is thought to represent peripheral resistance. An absence or lowering of EDV has been described by many authors in cases of IUGR (Milliez et al, 1983; Griffin et al, 1984; Jouppila and Kirkinen, 1984). It is thought to be secondary to an increase in peripheral vascular resistance at the fetal placental level. One centre reported an absence of the end diastolic velocities in normal pregnancies in the descending fetal aorta (Schulman et al, 1984). It is possible that the high pass filter level used in this study is higher than those used by us (150 Hz) and other centres, resulting in an absence of end diastolic velocities. A second explanation may be the attempt to obtain velocity waveforms from the descending aorta in the absence of real time imaging.

In our normal study, EDV and PI did not alter. However, the large S.D. values allow only gross changes to "zero" level (filter level) or a downward trend over a number of EDV and PI measurements to be interpreted as significant, as has become evident from our IUGR data.

In our IUGR group, the majority of birthweights were below the 5th percentile. In the case of symmetrical growth retardation (case 1), PV, EDV and PI were normal, except for a coincidental rise in EDV on one occasion. In the majority of asymmetrical IUGR (increased HC to AC ratio), PV and EDV were significantly reduced and PI significantly elevated. These findings have also been observed by other centres (Griffin et al, 1984). Case 6 had PV and EDV values that were lowered in such a way that, in association with the averaged velocity, a normal PI value was obtained. Whereas the reduction in EDV and rise in PI suggest increased peripheral vascular resistance, the low PV values may be determined by either an impaired cardiac contraction force or selective redistribution of the cardiac output to the upper part of the body (brain sparing effect), resulting in diminished flow through the descending aorta.

In 8 cases of fetal cardiac arrhythmia, a lowering of PV coincided with the onset of ultrasonic evidence of congestive cardiac failure, suggesting again that PV may reflect cardiac contraction force (Tonge et al, 1986).

Of interest is that in those patients where there was growth retardation, and the heart rate patterns were abnormal or subsequently became abnormal, the PV was always below 50-55 cm s^{-1} with the exception of case 11.

Case 11 had an abnormal heart rate pattern despite a normal PV. This patient was hypertensive and was treated with Methyl Dopa. It is possible that this medication might have had a positive inotropic action on the fetal myocardium and resulted in the normal PV value. Cases 8, 9 and 10 had PV values below 45 cm s^{-1}. Case 8 died within 5 minutes of birth. It weighed only 530 g. It was not delivered until 32 weeks, even in the presence of an abnormal heart rate pattern, because of the extreme IUGR and low gestational age.

Case 9 was seen on two occasions within 48 hours. The PV dropped from 55 cm s^{-1} to 33 cm s^{-1}. At the time of the second recording, decelerations were present on the heart tracing, and the fetus (Trisomy 13) died within 2 hours. It is perhaps surprising that the PI was elevated in this case, since normal placentation is usually present in trisomies. Case 10 also had a very low PV, absent EDV and elevated PI. Immediate LSCS was performed, as the heart rate pattern developed decelerations. A baby in fair condition was delivered weighing 800 g.

Finally, in case 12, PV progressed from a low normal value to 54.1 cm s^{-1}, EDV also progressed downwards to zero and PI gradually increased. Within 24 hours following the last measurement the heart rate tracing developed decelerations, and a LSCS was performed. The infant was delivered in good condition.

It can be concluded that IUGR is closely associated with reduced EDV and elevated PI. Whereas no correlation could be established between the severity of IUGR and the degree of EDV reduction and PI rise, PV may be a helpful indicator of fetal well being, in that very reduced PV levels below 50 cm s^{-1} to 55 cm s^{-1} are accompanied by or even precede abnormal heart rate patterns. More data are needed to substantiate these findings.

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5.2 **Doppler ultrasound assessment of cerebral blood flow in the human fetus**

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Published in British Journal of Obstetrics & Gynaecology, vol. 63: 471-475 (1986)

Summary

A mechanical sector and linear array real-time scanner combined with a pulsed Doppler system were used for recording the flow velocity waveform in the internal carotid artery, the lower thoracic part of the descending aorta and the umbilical artery in the human fetus. A total of 42 fetuses in normal pregnancy and 9 growth retarded fetuses between 26 and 41 weeks of gestation was studied. In normal pregnancy the mean Pulsatility Index (PI) in the internal carotid artery varied between 1.5 and 1.6, in the descending aorta between 1.7 and 1.8 and in the umbilical artery between 0.7 and 1.3 ($p < 0.0005$). In the growth retarded cases the PI was reduced in the internal carotid artery and raised in the descending aorta and umbilical artery, suggesting an increased peripheral vascular resistance in the fetal body and placenta and a compensatory reduction in peripheral vascular resistance in the fetal cerebrum i.e. a brain-sparing effect in the presence of fetal hypoxia.

Introduction

With the introduction of combined real-time and pulsed Doppler ultrasound systems, a non-invasive method of measuring human fetal blood flow became available. In initial reports the technique of measuring volume blood flow in the umbilical vein (Gill, 1979) and fetal descending aorta (Eik-Nes et al, 1980) was presented. However, the errors which arise in assessing vessel diameter have resulted in attention turning to the qualitative interpretation of blood flow velocity waveforms, particularly as a possible method of predicting and diagnosing intra-uterine growth retardation (Griffin et al, 1984; Jouppila et al, 1984). The presence of increased cerebral blood flow during fetal hypoxia i.e. "brain-sparing effect" has been demonstrated under animal experimental conditions (Kjellmer et al, 1974; Peeters, 1978). In this communication we introduce a pulsed Doppler method for recording the flow velocity waveform in the internal carotid artery in the human fetus and compare this flow velocity waveform with that obtained in the lower thoracic part of the fetal descending aorta and the umbilical artery.

Material and Methods

A Diasonics CV 400 mechanical sector scanner was used to locate the internal carotid artery at the level of the bifurcation into the middle and anterior cerebral artery. To arrive to this particular level, we first obtained the standard plane for measuring the biparietal diameter. This plane includes the thalamus and the cavum

of the septum pellucidum; the middle cerebral artery can be seen pulsating at the level of the insula. The section should be symmetrical with respect to the midline and is best demonstrated when the fetal head is in the occipitotransverse position. In the next step the transducer was moved in a parallel fashion towards the base of the skull until one arrives at a plane which demonstrates a heart-shaped cross-section of the brainstem with the anterior lobes representing the pedunculi cerebri. Anterior to this heart-shaped structure, on either side of the midline, an oblique cross-section of the internal carotid artery as it divides into its middle and anterior cerebral branches can be seen as shown in Fig. 1. The sample gate of the Diasonics

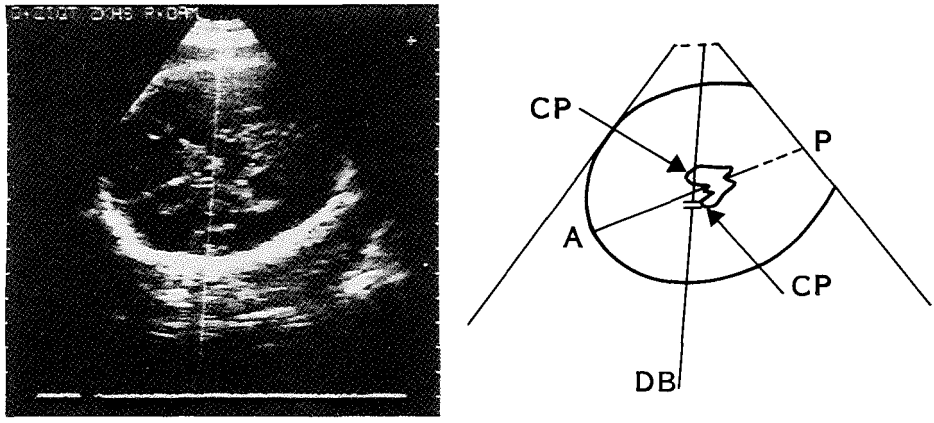

Figure 1. Cross-section through the fetal head at the level of the brain stem (heart-shaped structure) showing the cerebral peduncles (CP). The = sign in the Doppler beam path (DB) represents the Doppler sample gate positioned over an oblique cross-section of the internal carotid artery at 30 weeks of gestation; A = anterior; P = posterior.

CV 400 pulsed Doppler (carrier frequency: 3 MHz; length of sample volume: variable; beam width: 2 mm) was placed over the internal carotid artery and a maximum flow velocity waveform was recorded (Fig. 2). The degree of pulsatility of the waveform was quantified by calculating the Pulsatility Index (PI) which is defined as the difference between peak systolic and end-diastolic values divided by the averaged maximum flow velocity (Gosling and King, 1975). The maximum flow velocity waveforms in the umbilical artery and lower thoracic level of the fetal descending aorta were obtained according to the methods first described by McCallum et al (1978) and Eik-Nes et al (1980). Whereas the Diasonics CV 400 was successfully used for recording of the umbilical artery waveform, this equipment was not suitable for documentation of the aortic waveform due to the fact that the Doppler beam nearly always intersected the fetal descending aorta at unacceptable angles of between 70° and 90°. Instead a combined linear array real-time (Organon Teknika) and pulsed Doppler system (PEDOF, carrier frequency: 2 MHz; sample volume length: 8 mm; beam width: 12 mm) was employed whereby the angle between Doppler probe and fetal descending aorta was less than 50°. In all three flow velocity waveforms, the PI was calculated over five consecutive cardiac cycles.

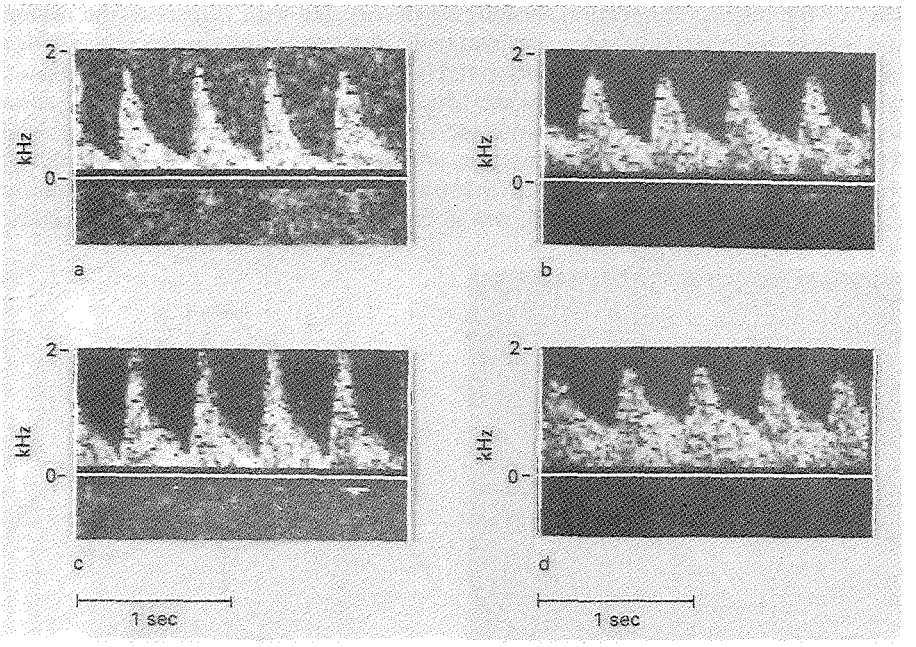

Figure 2. Flow velocity waveform in the fetal internal carotid artery during normal pregnancy and IUGR at 29 weeks (a and b) and 37 weeks of gestation (c and d).

The reproducibility of the flow velocity waveform recordings in the internal carotid artery was established as follows: the maximum flow velocity waveform was measured 10 times within 24 hours in three individual fetuses. The mean PI of each of these recordings was calculated and the mean SD determined.

A total of 42 normal pregnancies between 26 and 41 weeks was studied. In two subjects we failed to obtain a satisfactory flow velocity waveform in the internal carotid artery due to the occipito-anterior position of the fetal head, leaving 40 pregnancies for further evaluation. Birthweights were between the 10th and 90th percentile for gestational age according to Kloosterman's Tables (1970) corrected for maternal parity and fetal sex. PI data were equally divided ($n = 10$) into four age groups: 26-29; 30-33; 34-37 and 38-41 weeks. In each age group the mean $\pm$ 1 SD of the PI values for each of the three flow velocity waveforms was calculated. Differences in mean PI between two age groups were tested by the Mann-Whittney's rank sum test.

So far 9 cases of intra-uterine growth retardation (IUGR) have been studied. IUGR was defined by: a) flattening of the growth pattern resulting in a clinical discrepancy of more than two weeks of fundal height on two successive appointments combined with ultrasonic findings of upper abdominal circumference measurement below the 10th percentile in association with normal or reduced head circumference measurement (Campbell, 1976); b) postnatal confirmation by a birthweight below the 10th

percentile for gestational age according to Kloosterman's Tables (1970) corrected for maternal parity and fetal sex. All flow velocity waveform recordings were obtained during fetal apnoea.

Results

In about 95% of the cases an individual measurement of the PI in the internal carotid artery fell within 0.13 of the expected mean indicating an acceptable degree of reproducibility. During normal pregnancy, there is continuous forward flow throughout the cardiac cycle in the internal carotid artery (Fig. 2). Table I gives the mean ± 1 SD for the PI in the internal carotid artery (ICA), descending aorta (DAO) and umbilical artery (UA) for the four age groups. Mean PI in the ICA ranges between 1.5 and 1.6, in the DAO between 1.7 and 1.8 and the umbilical artery between 0.7 and 1.3. The latter difference is statistically significant ($p < 0.001$). The PI and birthweight percentiles for the IUGR group are shown in Table II. The PI values of the IUGR group were compared to the PI values of the normal population. The most striking feature was the marked reduction (below 1 SD of the normal mean PI for gestational age) of the PI in the internal carotid artery with a concomitant rise (above 1 SD) in the descending aorta and umbilical artery.

Table I. Pulsatility index in the internal carotid artery (ICA), descending aorta (DAO) and umbilical artery (UA) in 40 normal pregnancies. Results are means ± SD.

	PULSATILITY INDEX		
Gestational age (wks)	ICA	DAO	UA
26-29	1.6 ± 0.2	1.8 ± 0.2	1.3 ± 0.1
30-33	1.6 ± 0.2	1.8 ± 0.2	1.0 ± 0.2
34-37	1.5 ± 0.2	1.8 ± 0.2	0.8 ± 0.1
38-41	1.5 ± 0.2	1.7 ± 0.2	0.7 ± 0.2

Table II. The pulsatility index in the internal carotid artery (ICA), descending aorta (DAO) and umbilical artery (UA) as well as the birthweight percentile in nine pregnancies with intrauterine growth retardation. Note the marked reduction in PI for the ICA and marked increase in PI for the DAO and UA. * = value between 1 SD and 2 SD of the normal population mean (see Table I): ** = value > 2 SD of the normal population mean (see Table I).

		PULSATILITY INDEX			
Patient no.	Gestational age (wks)	ICA	DAO	UA	Birthweight percentile
1	28	1.0*	3.1**	2.7**	< 2.3
2	28	0.9**	2.5**	1.7**	< 5
3	29	1.0**	2.6**	1.8**	< 2.3
4	30	1.3*	2.7**	2.1**	< 5
5	34	1.0**	2.4**	1.5**	< 2.3
6	36	0.8**	2.3**	1.3**	< 2.3
7	37	0.9**	2.0*	1.1**	< 5
8	37	0.8**	3.0**	1.5**	< 2.3
9	37	1.0**	2.5**	1.3**	< 5

Discussion

The blood flow velocity profile in the internal carotid artery plays an important role in the qualitative assessment of cerebral blood flow. The observed elevation of this blood flow velocity profile above the baseline throughout the cardiac cycle in the normal population confirms the existence of a low peripheral vascular resistance in the fetus. The PI data in Table I suggest that during normal development the peripheral vascular resistance is the same for the fetal body and cerebrum and does not change significantly during the third trimester of pregnancy. This is in agreement with the observation that in this period of pregnancy cardiac output as well as volume blood flow in the descending aorta and umbilical vein per kg fetal bodyweight stay fairly constant (Vosters, 1983; Maršál et al, 1984a). The reduction in PI in the umbilical artery, as has been observed by others (Stuart et al, 1980; Reuwer et al, 1984; Trudinger et al, 1985) corroborates the finding of low vascular resistance, decreasing with advancing gestational age, in the ovine placenta (Dawes, 1968).

The regulation of local blood flow in many body tissues is determined by the need of the tissues for nutrients. The oxygen demand of the tissues can be considered as being the most important local regulator of tissue blood flow (Guyton et al, 1964). Several workers have studied the role of available oxygen in the regulation of cerebral blood flow in the fetus under animal experimental conditions. It was noticed that hypoxic stress always leads to an increase in cerebral blood flow (Kjellmer et al, 1974; Peeters, 1978). In our study of intrauterine growth retardation, we observed a marked elevation in PI in the descending aorta and umbilical artery and a marked decrease in PI in the internal carotid artery. The alterations in PI indices are predominantly due to changes in end-diastolic flow velocity. From Fig. 2, it can be seen that the reduction in PI in the internal carotid artery is mainly determined by an elevation of end-diastolic flow velocity.

The presented data suggest an increased peripheral vascular resistance in the fetal body and placenta and a compensatory reduction in peripheral vascular resistance in the fetal cerebri i.e. a "brain-sparing effect" in the presence of fetal hypoxia. A similar finding was demonstrated by Maršál et al (1984b) in the common carotid artery. The same group has also stated (personal communication) that they do not observe alteration in the shape of the flow velocity waveforms when progressing cranially. However, we feel that the common carotid artery is less representative of cerebral blood flow since it gives rise to the external carotid artery. Also in our experience, the common carotid artery which is obtained from a longitudinal scan of the head and neck area is less easy to visualize due to the often curved position of this area particularly, when the fetal spine is anterior. Only twice in our study were we unable to be certain that we had obtained internal carotid artery flow velocity waveforms. This was because the position of these fetuses was occipito-anterior and the anatomical plane described earlier was not clearly defined. Finally, we think that the preliminary data presented in this communication justify a further study on the sensitivity and specificity of the PI in the internal carotid artery with respect to the early diagnosis of intrauterine growth retardation.

Acknowledgement

We are grateful to Diasonics/Sonotron for the use of the Diasonics CV 400 in this particular study.

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5.3 Severe intrauterine growth retardation; assessment of its origin from fetal arterial flow velocity waveforms

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Published in European Journal of Obstetrics & Gynecology Reprod. Biology, vol. 22:23-28 (1986)

Summary

Doppler blood flow velocity waveforms in the umbilical artery and fetal internal carotid artery were recorded in a total of 10 patients with severe intrauterine growth retardation (IUGR) and marked oligohydramnios to establish a fetal or utero-placental origin of IUGR. Gestational age varied between 28 and 37 weeks. Negative maternal serology ruled out fetal infections. In six patients, IUGR was associated with abnormal flow velocity waveforms indicating utero-placental insufficiency. Following delivery, these infants showed no structural defects; moderate to marked placental infarction was documented in 4 out of 6 cases. In the remaining four patients, IUGR was associated with normal flow velocity waveforms, suggesting a fetal origin of the IUGR. Following delivery, all four infants revealed structural defects, only one of which was diagnosed prenatally. Twice an abnormal karyotype was the underlying cause. There was no placental infarction. These preliminary data suggest that combined recording of the flow velocity waveform in the above-mentioned vessels may provide valuable additional information as to the cause of IUGR and as such be helpful in determining obstetric management.

Key words: fetal blood flow velocity waveforms, Doppler ultrasound, intrauterine growth retardation, oligohydramnios

Introduction

Severe intrauterine growth retardation (IUGR) associated with marked oligohydramnios constitutes a considerable problem with respect to establishing the cause of IUGR and subsequent obstetric management. Particularly in the presence of structural defects, IUGR is associated with a poor fetal outcome. Whereas prenatal ultrasound has shown to be of considerable value in the detection of fetal structural anomalies, the presence of marked oligohydramnios may greatly restrict the quality of fetal imaging even with present high-resolution real-time scanners. Calculation of the head-to-abdomen circumference (H/A) ratio (Campbell and Thoms, 1977) has been helpful in differentiating between asymmetrical and symmetrical growth retardation. Whereas the former usually is a result of diminished uteroplacental function, the latter mostly suggests a fetal origin of the growth retardation. However, in the presence of severe IUGR, particularly associated with marked oligohydramnios, it may be difficult to obtain a reliable measurement of the head and/or upper-abdominal circumference.

With the introduction of combined real-time and Doppler Ultrasound systems, a simple non-invasive method of measuring human fetal blood flow velocities has become available (Eik-Nes et al, 1980). End-diastolic blood flow velocity values have been shown to be reduced at the lower thoracic level of the fetal descending aorta (Jouppila et al, 1984; Griffin et al, 1984) and umbilical artery (Reuwer et al, 1984; Trudinger et al, 1985a) and raised in the fetal internal carotid artery (Wladimiroff et al, 1985a) in the presence of IUGR, secondary to reduced placental function.
The aim of the present study was to establish to what extent blood flow velocity measurements in the umbilical artery and fetal internal carotid artery allow differentiation between fetal and uteroplacental pathology in the presence of severe IUGR and oligohydramnios.

Material and Methods

A total of 10 patients with severe IUGR and marked oligohydramnios was referred to our centre in order to try and establish a fetal or uteroplacental cause of the IUGR. Gestational age was certain, as determined by early crown-rump length or BPD measurement and varied between 28 and 37 weeks. IUGR was defined as:

a. a clinical discrepancy of more than two weeks in fundal height on two successive antenatal appointments combined with ultrasonic findings of upper abdominal and head circumference measurements below the 5th percentile according to the normograms established by Campbell and Wilkin (1975) and Campbell (1976). Head to abdominal (H/A) ratio values were subsequently calculated according to the method of Campbell and Thoms (1977).
b. postnatal confirmation by birthweight below the 5th percentile for gestational age according to Kloosterman's Table (Kloosterman, 1970), corrected for maternal parity and fetal sex.

Marked oligohydramnios was defined as being present if a pocket of amniotic fluid greater than 1 cm in broadest diameter was not revealed on real-time scanning (Manning et al, 1981).
Following maternal blood screening for infections, for example toxoplasmosis, cytomegalovirus, herpes, rubella and syphylis, a detailed 2D real-time search for the presence of fetal structural anomalies was carried out in each subject using a mechanical sector scanner (Diasonics CardioVue 100, 5 MHz transducer). This was followed by the recording of the blood flow velocity waveform in the umbilical artery and internal carotid artery over at least five consecutive cycles using a combined mechanical sector and pulsed Doppler system (Diasonics CardioVue 400, 3 MHz Doppler transducer) for calculation of the Pulsatility Index as first described by Gosling and King (1975). Amniocentesis for fetal karyotyping was considered in each case.

Results

Tables I and II represent the pertinent details relative to the 10 patients. All patients had severe IUGR and marked oligohydramnios according to the criteria established at the onset of the study, rendering it impossible to carry out amniocentesis

Table I. Gestational age, head-to-abdomen (H/A) ratio, prenatal diagnosis of structural defects, mode of delivery and fetal outcome in six patients with abnormal Pulsatility Index (PI) values in the umbilical artery (UA) and fetal internal carotid artery (ICA). H/A ratio = head-to-abdomen circumference ratio; ↑ = raised (> + 2 SD), ? = measurement failed; ↓ = reduced (> − 2 SD); LSCS = Caesarean section.

		Ultrasonic findings				
Pat. no.	gest. age (wks)	H/A ratio	Structural defects	PI_{UA}	PI_{ICA}	Mode of delivery; fetal outcome
1	28	?	—	↑	↓	LSCS at 30 wks; ♂ 870 g (< 2.3 perc), healthy; < 10% plac. infarction
2	29	↑	—	↑	↓	IUD at 31 wks; vag. delivery; ♂ 800 g (< 2.3 perc), no structural defects; 50% plac. infarction
3	31	?	—	↑	↓	LSCS at 31 wks; ♀ 700 g (< 2.3 perc), no structural defects, † on day 6; > 50% plac. infarction
4	33	↑	—	↑	↓	LSCS at 33 wks; ♂ 1170 g (< 2.3 perc), healthy; c. 10% plac. infarction
5	34	↑	—	↑	↓	LSCS at 34 wks; ♂ 1180 g (< 5 perc), no structural defects, healthy; c. 20% plac. infarction
6	37	↑	—	↑	↓	vag. delivery at 38 wks; ♀ 1590 g (< 2.3 perc), healthy; c. 20% plac. infarction

Table II. Gestational age, head-to-abdomen (H/A) ratio, prenatal diagnosis of structural defects, mode of delivery and fetal outcome in four patients with normal Pulsatility Index (PI) values in the umbilical artery (UA) and fetal internal carotid artery (ICA). H/A ratio = head-to-abdomen circumference ratio; N = normal; LSCS = Caesarean section; MCA = multiple congenital abnormalities: slight hydrocephaly, spina bifida occulta, syndactyly, pulmonary atresia, scalp defect.

		Ultrasonic findings				
Pat. no.	gest. age (wks)	H/A ratio	Structural defects	PI_{UA}	PI_{ICA}	Mode of delivery; fetal outcome
7	29	N	absent kidneys; no bladder filling	N	N	IUD at 30 wks; vag. delivery; ♀ 1010 g (< 5 perc), bilateral renal agenesis; no plac. infarction
8	29	N	—	N	N	premature vag. delivery at 30 wks, ♀ 725 g (< 2.3 perc), MCA + triploidy (69 XXX); no plac. infarction
9	31	N	—	N	N	LSCS at 37 wks, ♀ 1740 g (< 2.3 perc), abnormally shaped ears + fingers, VSD, trisomy 18; no plac. infarction
10	32	N	—	N	N	LSCS at 36 wks, ♀ 1550 g (< 2.3 perc), microcephaly, glaucoma, buphtalmus; no plac. infarction

for fetal karyotyping. There was no serological evidence of maternal infections. In patients 1-6 (Table I), no fetal structural defects were observed, the Pulsatility Index in the umbilical artery (PI_{UA}) was significantly raised (> + 2 SD) and the Pulatility Index in the internal carotid artery (PI_{UA}) significantly reduced (> − 2 SD) according to the normal values reported by Wladimiroff et al (1985a). The fetal H/A ratio was significantly raised (> + 2 SD) in four out of six cases according to the normogram by Campbell and Thoms (1977); no upper-abdominal circumference could be obtained in the remaining two cases. Caesarian section was carried out in patients 1, 3, 4 and 5 because of pathological fetal heart rate tracings, which were characterized by loss of beat-to-beat variability and appearance of recurrent decelerations. Fetal birthweight was always below the 5th percentile. Placental infarction was moderate (c.20%) in patients 5 and 6 and marked (≥ 50%) in patients 2 and 3. The overall mortality was 33%.
In patients 7-10 (Table II), prenatal ultrasound examination revealed renal agenesis (no 7), whereas PI_{UA} and PI_{ICA} were within normal limits in all instances. H/A ratios were normal in all four patients. Following delivery, fetal congenital structural defects were present in all four patients, twice as a result of an abnormal karyotype (69XXX; trisomy 18). Caesarian section was performed in patients 9 and 10 following the appearance of pathological heart rate tracings. Fetal birthweight was always below the 5th percentile. The placentas demonstrated no infarctions. The overall mortality was 100%.

Discussion

In the present study, all patients revealed marked oligohydramnios associated with severe IUGR, constituting a high-risk group with a high perinatal mortality rate. The raised PI_{UA} values in patients 1-6 typically represent elevated umbilical placental flow resistance (Reuwer et al, 1984; Trudinger et al, 185a). The severity of IUGR cannot be closely correlated with the percentage (macroscopic) placental infarction, and only in four out of these six patients could moderate to marked placental infarction be established as an indicator of uteroplacental insufficiency. Further evidence of a uteroplacental cause of IUGR in patients 1-6 is provided by the reduced PI_{ICA} values reflecting a brain sparing effect in the presence of chronic fetal hypoxia (Wladimiroff et al, 1985a). High resistance Doppler flow velocity waveforms have recently been reported in the arcuate artery (Campbell et al, 1983) and in the interal iliac artery (Trudinger et al, 1985b) in IUGR. The exact relationship between these maternal velocity waveforms and velocity waveforms in the umbilical artery has not been clarified yet. In patients 7-10 entirely normal PI_{UA} and PI_{ICA} values were obtained suggesting a fetal origin of the IUGR. Fetal infection was unlikely since maternal serology for toxoplasmosis, rubella, cytomegalovirus, herpes and syphilis was negative. Only in patient 7 was a fetal structural defect established (prenatally). The nature of the fetal structural defects in patients 8 and 9 was such that in the presence of marked oligohydramnios prenatal detection was impossible. Fetal microcephaly (patient 10) was missed as a result of normal H/A ratio values. IUGR may also be associated with chromosomal defects (Johnson et al, 1982; Wladimiroff et al, 1985b). Indeed, structural defects were twice associated with an abnormal karyotype which was not diagnosed prenatally

due to the lack of amniotic fluid, but was suspected in the presence of normal waveforms.

Trudinger and Cook (1985) observed both normal and abnormal umbilical artery waveforms in IUGR associated with major fetal abnormalities. Normal umbilical artery waveforms were observed in fetuses with a low placental/fetal weight ratio reflecting a low fetal growth potential. Whereas in our study normal H/A ratios in patients 7-9 also indicate low fetal growth potential and are associated with normal PI_{UA} values, the findings by Trudinger and Cook (1985c) suggest that umbilical artery flow measurements alone may not always be helpful in differentiating between IUGR resulting from deprivation of oxygen or nutrient supply and IUGR associated with genetic abnormality or fetal infection. The same authors postulate that a process of obliteration of small arteries in the placenta may be triggered by the abnormal fetus.

Abnormal changes in H/A ratio are usually determined by the occurrence of the brain sparing effect and as such the H/A ratio provides reliable information as to the cause of IUGR.

However, in the presence of marked oligohydramnios it may be difficult to obtain reliable abdominal circumference measurements, as has been shown in our study. The PI_{ICA} being a more direct indicator of the brain sparing effect, is easier to obtain under these circumstances. In conclusion, we feel that in the presence of severe IUGR and marked oligohydramnios combined calculation of the PI_{UA} and PI_{ICA} should provide valuable additional information as to the cause of the IUGR. Normal umbilical artery and internal carotid artery PI values should alert the obstetrician to the possible presence of severe fetal structural abnormality with or without abnormal karyotype.

Acknowledgements

We would like to thank all colleagues for referring their patients to our Ultrasound Unit. We are particularly grateful to Diasonics/Sonotron for the use of the Diasonics CV 400 in this study.

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Chapter 6

CONCLUSIONS

The inaccessibility of the human fetus is the greatest obstacle in measuring volume blood flow. Doppler ultrasound, in combination with real time imaging, provided the opportunity to study and measure volume blood flow in the human fetus non-invasively.

Volume blood flow measurements have two major components, namely blood flow velocity and vessel diameter. Further, when volume blood flow is conventionally expressed in ml min^{-1} kg^{-1}, a third component arises: fetal weight. The ultrasound estimation of both fetal weight and vessel diameter is subject to such major inaccuracies that any changes in volume blood flow should be interpreted with great care.

Chapter 2 provides information on ways in which the sources of error can be minimised, and ways in which the accuracy of any measurement can be enhanced. Despite these improvements in technique, major limitations and pitfalls still exist in volume blood flow measurement. Therefore only trends in volume blood flow can be interpreted as significant and even then they are only guidelines.

Trends that are of significance have been presented, however. Changes in volume blood flow with advancing gestational age are due almost entirely to changes in the dimensions of the fetal cardiovascular system. Trends in volume blood flow with varying heart rates provide evidence of the existence of the Frank Starling mechanism in the human fetal myocardium.

The possibility of using volume blood flow measurements as a clinical tool now arises. By sequential measurements, the response of a fetus to anti-arrhythmic therapy can be monitored. Further studies are required to test the efficacy of this suggestion.

The aetiology of intrauterine growth retardation remains a major obstetric puzzle. Studies should not only be directed towards solving this problem, but also towards the detection of a compromised fetus as early as possible to optimise ante-natal care. The studies presented have provided data that show that blood flow velocity recordings from the fetal descending aorta are a sensitive agent in assessing and monitoring the well being of a growth retarded fetus. As a screening tool, however, blood flow velocity recordings from the umbilical artery are more suitable because of the relative ease and speed of recording the signals.

Blood flow velocity recordings from the internal carotid artery in conjunction with umbilical artery recordings have shown that the "brain-sparing effect" is functional in the growth retarded human fetus. They have also been shown to play a role in warning the obstetrician of either major fetal structural or chromosomal abnormality.

An incomplete chart of the fetal circulation can be drawn up from the data presented in this thesis. With the advent of more sophisticated equipment, this chart will become more complete. A complete "mapping" will give the obstetrician greater insight into the pathophysiology of abnormal pregnancy and will serve to enhance antenatal care.

SUMMARY

Chapter 1.
There has been an interest shown in the study of the human fetal circulation for hundreds of years. The inaccessibility of the human fetus has prevented research workers measuring volume blood flow directly, so most of our current knowledge is derived from animal experimental work. The advent of Doppler ultrasound has enabled non-invasive measurements of volume blood flow in the human fetus to be carried out. The main aims of the research work were to develop a method of measuring volume blood flow in the lower thoracic level of the fetal descending aorta with particular emphasis on the pulsatile character of the flow velocity and vessel diameter waveforms. Data on normal pregnancy were collected. The clinical importance of some factors affecting volume blood flow – namely fetal cardiac arrhythmias and intrauterine growth retardation, is stressed.

Chapter 2.
The techniques and equipment that were used for volume blood flow measurements in the lower thoracic level of the fetal descending aorta are described. The potential sources of error are discussed and the methods by which these are minimised are described. Two major drawbacks of volume blood flow measurements are the assessment of fetal weight by ultrasound and the measurement of the aortic diameter. A pulsatile vessel diameter waveform is obtained in order to incorporate the pulsatile nature of the vessel wall movement with the blood flow velocity changes throughout the cardiac cycle. The two waveforms were compared by a fetal ECG.
A satisfactory alternative for comparing the two waveforms is the first derivative method.
The mean blood flow velocity calculated from a spectrum analyser is not significantly different from the mean blood flow velocity obtained from the "mean velocity estimator".

Chapter 3
Volume blood flow data were measured from a preliminary study of twenty normal late pregnancies. With advancing gestational age, volume blood flow and aortic stroke volume increases. Changes in the pulsatile vessel profile are responsible for these increments. Blood flow velocity does not change with increasing gestational age.

Chapter 4
Three studies of fetal cardiac arrhythmia and its effect on volume blood flow in the lower thoracic level of the fetal descending aorta are presented.
Alterations in heart rate did not alter volume blood flow in the descending aorta. A

reduction in heart rate was associated with an increase in aortic stroke volume, peak blood flow velocity, acceleration of blood flow velocity and maximum diameter change. These alterations were reversed in the presence of a tachyarrhythmia, although the changes were less marked. The fetal myocardium is able to maintain blood flow to the fetus within the physiological limits of the Frank Starling mechanism. Peak flow velocity and aortic stroke volume alter in a similar way with varying heart rates.
Two dimensional ultrasound and M-mode echocardiography are useful tools in the assessment of a fetal cardiac arrhythmia, providing information about cardiac size, structure and rhythm. From a study of thirty patients, it can be stated that ectopic beats are generally benign. A bradyarrhythmia when associated with a cardiac structural abnormality is sinister and is more sinister than a tachyarrhythmia in association with a cardiac structural defect. Serial echocardiography is a means of monitoring transplacental treatment.

Chapter 5
Errors are inherent in volume blood flow measurements, so the articles presented in this chapter discuss qualitative changes in the blood flow velocity waveform in the presence of intrauterine growth retardation. Changes were investigated not only in the fetal descending aorta, but also in the internal carotid and umbilical arteries. The method by which blood flow velocity waveforms from the internal carotid artery are obtained is described.
End diastolic velocities are reduced or even absent (filter level) in the presence of intrauterine growth retardation both in the fetal descending aorta and umbilical artery. The pulsatility index was raised in both vessels. For the internal carotid artery end diastolic velocities were increased, resulting in a reduced pulsatility index. This is evidence for the existence of the brain-sparing effect in the human growth retarded fetus. Normal blood flow velocity waveforms in the internal carotid and umbilical arteries in the presence of severe intrauterine growth retardation is suggestive of a severe fetal abnormality.

SAMENVATTING

Hoofdstuk 1
Reeds enkele eeuwen is aandacht besteed aan de circulatie van de humane foetus. De onbereikbaarheid van de humane foetus staat direct onderzoek naar de bloeddoorstroming in de weg. Het is daarom dat het merendeel van onze kennis afkomstig is van dierexperimenteel onderzoek. De invoering van Doppler ultrageluid maakt het mogelijk om op non-invasieve wijze metingen aan de bloeddoorstroming bij de humane foetus te verrichten. Het voornaamste doel van het onderzoek was het meten van bloedstroom volumina in het laag thoracale deel van de foetale aorta descendens, waarbij de aandacht speciaal gericht was op het pulsatiele karakter van het bloedstroomsnelheids en vaatdiameter profiel. Normaalwaarden in het derde zwangerschapstrimester werden verkregen. Het klinisch belang van een aantal factoren, zoals foetale hartaritmie en intrauteriene groeivertraging op de bloeddoorstroming, wordt benadrukt.

Hoofdstuk 2
De technieken en apparatuur gebruikt voor bloeddoorstromingsmetingen in het laag thoracale deel van de foetale aorta descendens worden beschreven. De potentiële foutenbronnen en de wijze waarop deze tot een minimum kunnen worden beperkt worden besproken. Twee grote nadelen verbonden aan bloed volumina metingen zijn de bepaling van het foetale gewicht d.m.v. ultrageluid en de meting van de vaatdiameter. Een methode werd ontwikkeld voor registratie van het pulsatiele vaatdiameter profiel teneinde gedurende de gehele hartcyclus de pulsatiliteit van de vaatdiameter met die van de bloedstroomsnelheid te kunnen vergelijken. Deze vergelijking vond plaats m.b.v. het foetale ECG. Als een volwaardig alternatief voor een dergelijke vergelijking werd de "eerste afgeleide" van de eerder genoemde profielen ingevoerd.
De gemiddelde bloedstroomsnelheid berekend m.b.v. spectraal analyse was niet beduidend verschillend van die verkregen via de zgn. "mean velocity estimator".

Hoofdstuk 3
Bloedstroom volumina werden berekend in 20 normale 3e trimester zwangerschappen. Bij het vorderen van de zwangerschapsduur neemt het minuut- en slagvolume in de aorta toe. Veranderingen in het pulsatiele vaatdiameter profiel zijn hiervoor verantwoordelijk. De bloedstroomsnelheid blijft bij het vorderen van de zwangerschapsduur ongewijzigd.

Hoofdstuk 4
In dit hoofdstuk worden drie onderzoeken naar de foetale hartaritmie en het effect op de bloeddoorstroming in het laag thoracale deel van de foetale aorta descendens besproken. Veranderingen in de hartfrequentie leiden niet tot wijzigingen in het minuutvolume in de aorta descendens. Een afname in de hartfrequentie ging echter

gepaard met een toename in het slagvolume, de acceleratie en het maximum van de bloedstroomsnelheid alsmede toename in maximale verandering van de vaatdiameter. In mindere mate werd een afname van deze parameters waargenomen in de aanwezigheid van een tachyaritmie. Het foetale myocard is in staat om de foetale bloeddoorstroming binnen de fysiologische grenzen van het Frank Starling mechanisme redelijk constant te houden. Twee dimensionale real-time en M-mode echocardiografie zijn zeer bruikbaar gebleken bij het vaststellen van de aard van een foetale hartaritmie en het verkrijgen van informatie over de grootte, de structuur en het ritme van het hart. Uit een onderzoek bij 30 zwangeren kan worden gesteld dat extrasystoliën in het algemeen goedaardig zijn. Een bradyaritmie welke gepaard gaat met een structurele hartafwijking heeft een slechte prognose, dit is in mindere mate het geval voor de gecombineerde aanwezigheid van een tachyaritmie en structureel hartdefect. Echocardiografie is zinvol gebleken bij de bewaking van transplacentaire behandeling van foetale hartaritmieën.

Hoofdstuk 5
Zoals reeds eerder gesteld, kleven aan bloedstroom volumina metingen bezwaren. De artikelen gepresenteerd in dit hoofdstuk bespreken de kwalitatieve veranderingen in de bloedstroomsnelheidscurven in de aanwezigheid van intrauteriene groeivertraging. Veranderingen werden niet alleen nagegaan in de foetale aorta descendens maar ook in de arteria carotis interna en arteria umbilicalis. De methode tot het verkrijgen van bloedstroomsnelheids profielen in de foetale arteria carotis interna wordt beschreven. De einddiastolische bloedstroomsnelheid was afgenomen of zelfs afwezig (beneden het filter niveau) in de aanwezigheid van intrauteriene groeivertraging zowel in de foetale aorta descendens als in de arteria umbilicalis. De pulsatiliteits index was in beide vaten verhoogd. In de foetale arteria carotis interna echter werd een toename van de einddiastolische bloeddoorstroomsnelheid gezien, resulterend in een afname van de pulsatiliteits index. Deze bevinding is suggestief voor het bestaan van het zgn. hersensparend effect in de humane groeivertraagde foetus. Normale bloedstroomsnelheidsprofielen in de arteria carotis interna en arteria umbilicalis bij zeer uitgesproken intrauteriene groeivertraging suggereren de aanwezigheid van een ernstig foetaal structureel defect.

ACKNOWLEDGEMENTS

The research work described in this thesis was performed in the Department of Obstetrics and Gynaecology, University Hospital - Dijkzigt, in close association with the Central Research Laboratory, Rotterdam.
Throughout the study period, I have been very fortunate in having had the continuous support, encouragement and advice of Professor Dr. J.W. Wladimiroff, to whom I am particularly grateful.
I should like to thank Professor Dr. Ir. N. Bom for his constructive criticisms during the discussions of the thesis.
For their willingness to be members of the committee and for their helpful comments, I should like to thank Professor Dr. J.R.T.C. Roelandt and Professor Dr. A.A. Haspels.
Piet Struijk has been invaluable in providing not only essential technical advice, but also essential insight into what goes on 'behind the screen'.
The computer programme was designed by Cor van Kooten.
Marja Noordam has been a tremendous help both as a student assistent and an interpreter.
I should like to thank Sylvia Noordzij for her excellent and speedy typing of my thesis.
Also, I want to thank all the co-authors of the articles. The articles could not have been written without the help and co-operation of the patients.
I am grateful to Diasonics/Sonotron for their generous financial support.
Finally, without the support, forbearance and patience of my husband, I could not have undertaken any of the work necessary for this thesis. I will always be indebted to him.

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