

Power spectrum analysis of heart rate and blood flow velocity variability measured in the umbilical and uterine arteries in early pregnancy: a comparative study

P. C. STRUIJK, N. T. C. URSEM, J. MATHEWS*, E. B. CLARK†, B. B. KELLER‡ and J. W. WLADIMIROFF

Department of Obstetrics and Gynaecology, University Hospital Rotterdam-Dijkzigt, The Netherlands, *Department of Electrical Engineering and †Department of Pediatrics, Primary Children's Medical Center, The University of Utah, Salt Lake City and ‡Department of Pediatrics, University of Kentucky, Kentucky, USA

KEYWORDS: Spectrum analysis, Umbilical artery, Uterine artery

ABSTRACT

Objective To compare power spectral derived variability parameters from the fetal side of the placental circulation with those from the maternal side of the placental circulation, during early pregnancy.

Methods Doppler velocity waveforms were obtained from both the umbilical and the uterine arteries in a study group of 40 pregnant women between 10 and 14 (n = 25) and 15 and 20 (n = 15) weeks of gestation. The coefficient of variation of both the beat-to-beat heart rate variability and the blood flow velocity variability was determined. The ratio of the integrated low-frequency components (< 0.2 Hz) and the integrated high-frequency components (> 0.2 Hz) from normalized power spectrum analysis (LH-ratio) was established, to reflect sympathovagal balance.

Results The coefficient of variation and LH-ratio of fetal heart rate variability constitute only a fraction of the same maternal heart rate variability parameters. Nevertheless a highly significant increase (P < 0.001) in LH-ratio was demonstrated with advancing gestational age. The coefficient of variation and LH-ratio of blood flow velocity variability were significantly lower in the fetal umbilical artery only in the 10–14-weeks' gestation group. Due to a decrease of the maternal uterine blood flow velocity variability parameters with advancing gestational age, statistically equal fetal and maternal values for coefficient of variation and LH-ratio were found in the 15–20 weeks' gestation group.

Conclusions The increase in LH-ratio of fetal heart rate variability indicates functional development of the fetal autonomic nervous system at 15–20 weeks' gestation. The umbilical blood flow velocity variability may be secondary to

maternal uterine arterial flow variability rather than due to primary changes in fetal cardiovascular function.

INTRODUCTION

Doppler velocimetry of the fetal circulation can accurately characterize cardiac and extracardiac arterial and venous blood flow velocities^{1,2}. Recently, we published the results of a study concerning the variability of both the fetal heart rate and velocity waveform in the umbilical artery during early human development^{3–5}. Variability analysis in the frequency domain typically requires long (at least 20 s) data records to resolve low (< 0.1 Hz) frequency content. Spectral analysis decomposes variability data in the frequency domain so that a relationship can be established between various frequency components and specific control processes. Typically, the adult heart rate power spectrum demonstrates heart rate variability concentrated in two principal frequency ranges, the high-frequency band (> 0.2 Hz) and the low-frequency band (< 0.2 Hz)^{6–9}. The high-frequency band reflects parasympathetic activity, whereas the low-frequency band is influenced by combined sympathetic and parasympathetic control⁶. Their ratio is thus a reflection of sympathovagal balance¹⁰.

Little information is available on the presence of sympathetic and parasympathetic control in the early developing fetus. Functional parasympathetic regulation of cardiovascular function has been suggested on the basis of a marked reduction in fetal heart rate at 10–15 weeks of gestation¹¹. Alternatively, an increase in fetal cardiac stroke volume due to improved cardiac function has been proposed as an explanation for these heart rate changes⁴. Since autonomic nervous activity causes frequency-specific alterations in the heart rate power spectrum, the power spectrum analysis of these fluctuations

Correspondence: Prof J.W. Wladimiroff, Department of Obstetrics and Gynaecology, University Hospital Rotterdam-Dijkzigt, Dr Molewaterplein 40, 3015 GD Rotterdam, The Netherlands (e-mail: breur@gyna.azr.nl)

Received 22-2-00, Revised 9-10-00, Accepted 5-1-00

provides a quantitative non-invasive means of assessing the functionality of cardiovascular control.

We measured umbilical and uterine flow velocity waveforms at 10–20 weeks of gestation to determine both maternal and fetal heart rate variability and flow velocity variability as parameters of functional control of the autonomic nervous system¹². The aim of the study was to establish maternal and fetal variability in heart rate and blood flow velocity to compare developing and mature systems for autonomic regulation of cardiovascular function.

MATERIALS AND METHODS

Subjects

A total of 40 women with a normal singleton pregnancy between 10 and 20 weeks of gestation participated in the study. Two different gestational age groups were enrolled into the study: 10–14 weeks (group 1; median 12 weeks; $n = 25$) and 15–20 weeks (group 2; median 16 weeks; $n = 15$). Each woman was included in the study only once. The Hospital Ethics Committee approved the study and women were enrolled following informed consent. Maternal age ranged between 15 and 41 years (median 30 years). Gestational age was estimated from the last menstrual period and confirmed by ultrasound measurement of the fetal crown–rump length (10–12 weeks) or biparietal diameter (12–20 weeks). All pregnancies were uncomplicated and resulted in a term delivery of a normal infant with a birth weight between the 10th and 90th centiles corrected for maternal parity and fetal sex¹³.

Doppler recordings

Ultrasound Doppler studies were performed with a Toshiba SSH 140 A (Toshiba corp., Medical Systems Division, Tokyo, Japan). A combined transvaginal real-time and pulsed Doppler system (carrier frequencies 6 MHz and 5 MHz, respectively) was used at 10–13 weeks of gestation and a combined trans-abdominal real-time and pulsed Doppler system (carrier frequencies 5.0 MHz and 3.75 MHz, respectively) was applied at 14–20 weeks of gestation. The system operates at power outputs of $< 100 \text{ mW/cm}^2$ spatial peak–temporal average in both imaging and Doppler modes by manufacturer's specification. All Doppler studies were performed with the women in the semirecumbent position, during fetal apnea. The Doppler recordings were performed by one examiner (N.T.C.U.). The high pass filter was set at 100 Hz to attenuate low-frequency components originating from the vessel wall and the sample volume length was set between 0.2 and 0.3 cm to cover the center of the umbilical or uterine artery. Flow velocity waveforms from the umbilical artery were obtained from the free-floating loop. For the uterine artery velocity waveforms, the transducer was placed in the lower lateral quadrant of the uterus on the placental side and angled medially until the cross-over of the main uterine artery and external iliac artery and vein could be identified. This cross-over was used as a reference point to identify the main uterine artery. In two-dimensional color Doppler mode, for both the umbilical and

the uterine arteries, the sample volume was placed at the point where the highest color Doppler velocity was seen, to ensure that the insonation angle was as close as possible to zero degrees. A high quality Doppler recording of 20-s duration was selected for each vessel in each patient. Umbilical and uterine artery flow velocity waveforms were obtained in sequence with a time interval between the Doppler recordings of the two vessels of less than 5 mins.

Data processing

Uterine artery and umbilical artery Doppler recordings were stored on sVHS video tape in PAL format using a Panasonic model AG7350 machine (Matsushita Electric Ind Co, Takatsuki, Osaka, Japan). The forward and backward audio signals were digitized at a sampling frequency of 12 kHz using an AD data acquisition board (LabPC + and BNC-2081 boards, National Instruments, Austin, TX, USA). A digital maximum velocity reconstruction method was used to estimate the maximum velocity envelope. A more detailed description of the maximum velocity reconstruction method has been published previously³.

The time-averaged velocity was calculated from recordings of 20-s duration and used as a threshold to determine the instantaneous heart rate as expressed by the reciprocal of the time interval between successive interpolated threshold crossings. This was followed by calculation of the time-averaged velocity per heartbeat (Figure 1). For both the umbilical artery and the maternal uterine artery, the mean and standard deviation for all heart beats occurring during the 20-s recording were calculated and the coefficient of variation (standard deviation/mean) was taken as a measure of heart rate variability or time-averaged flow velocity variability. In a previous intraobserver variability study, acceptable reproducibility was obtained⁴.

The beat-to-beat data points from all flow velocity waveforms were converted into time series using linear interpolation. After quadratic de-trending, these time series of 20 s were divided into 64 time intervals from which the mean values were taken as data points for spectral analysis, resulting in a frequency range of 0.05–1.6 Hz. For scaling purposes and to make the velocity tracings angle independent, the data points were expressed as percentages of the mean before Fourier

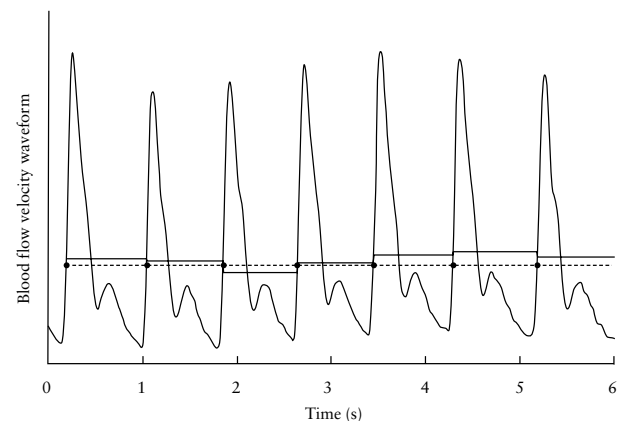


Figure 1 Maternal uterine blood flow velocity waveform at 12 weeks of gestation. Threshold level (dotted line), threshold crossings (●) and time averaged velocity per heartbeat (solid straight lines) are indicated.

transformation. Two frequency bands were defined: (i) a low-frequency band (0.05–0.2 Hz) and (ii) a high-frequency band (0.25–1.6 Hz)^{8,14}. The ratio between the integrated power of the low-frequency band and that of the high-frequency band was used for further analysis (LH-ratio).

The mean data for the two gestational age groups separately (10–14 weeks; 15–20 weeks) and the entire study period (10–20 weeks) as presented in Figures 2–5 were calculated

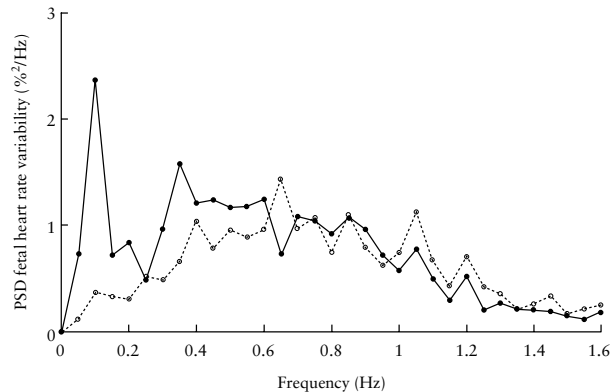


Figure 2 Mean power spectral distribution (PSD) for fetal heart rate variability at 10–14 weeks' gestation (○) ($n = 25$) and 15–20 weeks' gestation (●) ($n = 15$).

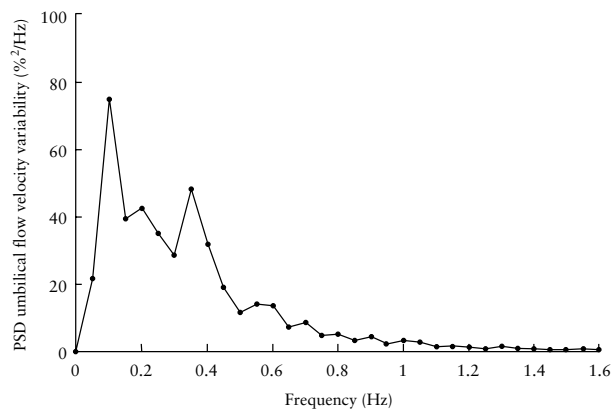


Figure 3 Mean power spectral distribution (PSD) for umbilical blood flow velocity variability at 10–20 weeks' gestation ($n = 40$).

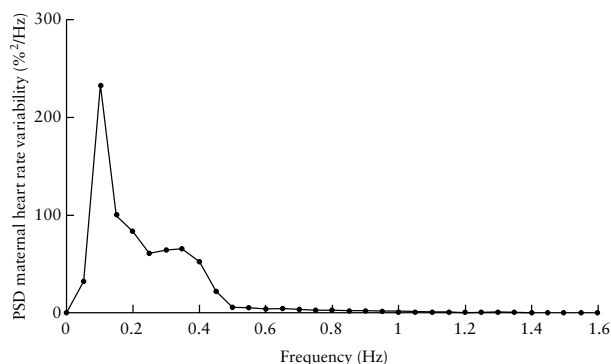


Figure 4 Mean power spectral distribution (PSD) for maternal heart rate variability at 10–20 weeks' gestation ($n = 40$).

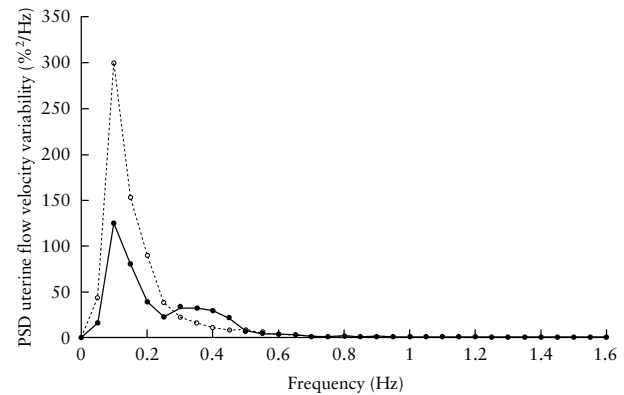


Figure 5 Mean power spectral distribution (PSD) for uterine blood flow velocity variability at 10–14 weeks' gestation (○) ($n = 25$) and 15–20 weeks' gestation (●) ($n = 15$).

by averaging the squared values of the Fourier transform for each frequency bin from 0.05–1.6 Hz.

Statistical analysis

The results were expressed as medians and interquartile ranges (QR). The Wilcoxon signed ranks test was used to compare differences between fetal and maternal derived coefficients of variation and LH-ratios. The Mann–Whitney test was used to compare coefficients of variation and LH-ratios between the two gestational age groups. A P -value of < 0.05 was considered to be statistically significant.

RESULTS

Heart rate variability and time-averaged flow velocity variability derived from umbilical artery and maternal uterine artery flow velocity waveforms are summarized in Tables 1 and 2. Averaged power spectral density of heart rate variability and time-averaged flow velocity variability determined from these two vessels are displayed in Figures 2–5.

Fetal circulation (umbilical artery)

The median fetal heart rate decreased significantly ($P < 0.001$) from 165 bpm (QR 156–171) at 10–14 weeks to 147 bpm (QR 143–154) at 15–20 weeks of gestation. The median coefficient of variation values demonstrate that fetal heart rate variability did not differ significantly between the two gestational age periods (Table 1). However, the median LH-ratio for fetal heart rate variability increased significantly ($P < 0.001$) from 0.05 at 10–14 weeks to 0.17 at 15–20 weeks of gestation (Table 2). Figure 2 shows that this result was derived from low intensities in the low-frequency range of the mean power spectral density distribution at 10–14 weeks, whilst the 15–20-week period was characterized by markedly increased low-frequency components.

The median coefficient of variation for the umbilical artery time-averaged flow velocity variability was similar between the two gestational age groups (Table 1). The median LH-ratio increased from 0.44 at 10–14 weeks to 0.85 at 15–20 weeks

Table 1 Coefficients of variation (%) for heart rate variability and blood flow velocity variability in the umbilical artery and the maternal uterine artery for two gestational age groups: 10–14 weeks ($n = 25$) and 15–20 weeks ($n = 15$)

	Gestation (weeks)		P-value (Mann–Whitney test)
	10–14	15–20	
Heart rate variability			
Umbilical artery	0.74 (0.65–0.91)	1.09 (0.53–1.47)	0.332
Uterine artery	4.23 (3.15–4.86)	4.48 (3.17–6.08)	0.472
P-value (Wilcoxon test)	< 0.001	0.001	
Blood flow velocity variability			
Umbilical artery	3.27 (2.53–4.50)	3.25 (1.84–4.85)	0.783
Uterine artery	4.76 (3.43–6.16)	3.35 (2.77–4.25)	0.015
P-value (Wilcoxon test)	0.013	0.955	

Table 2 Low-frequency band (0.05–0.2 Hz) to high-frequency band (> 0.2 Hz) ratio for heart rate variability and blood flow velocity variability in the umbilical artery and maternal uterine artery for two gestational age groups: 10–14 weeks ($n = 25$) and 15–20 weeks ($n = 15$)

	Gestation (weeks)		P-value (Mann–Whitney test)
	10–14	15–20	
Heart rate variability			
Umbilical artery	0.05 (0.03–0.09)	0.17 (0.09–0.45)	< 0.001
Uterine artery	0.95 (0.45–2.83)	1.33 (0.69–2.09)	0.740
P-value (Wilcoxon test)	< 0.001	0.001	
Blood flow velocity variability			
Umbilical artery	0.44 (0.31–0.96)	0.85 (0.45–1.44)	0.078
Uterine artery	4.11 (2.52–6.42)	1.31 (0.46–2.51)	0.001
P-value (Wilcoxon test)	< 0.001	0.496	

of gestation, but this difference did not reach statistical significance (Table 2). Therefore, the mean power spectral density distribution for the entire group of 10–20 weeks is shown (Figure 3).

Maternal circulation (uterine artery)

The median maternal heart rate of 75 bpm (QR 70–82) at 10–14 weeks did not differ significantly from that of 77 bpm (QR 74–87) at 15–20 weeks of gestation. No statistically significant difference existed between the two gestational age groups for both the median coefficient of variation (Table 1) and the median LH-ratio for maternal heart rate variability (Table 2). Figure 4 depicts the mean power spectral density distribution for time-averaged flow velocity variability for the total group of 40 fetuses at 10–20 weeks of gestation. A high-intensity peak in the low-frequency band with a second peak representing respiration frequency at 0.3–0.4 Hz, describes the frequency distribution of maternal heart rate variability. A statistically significant decrease ($P = 0.015$) was established for the median coefficient of variation regarding the time-averaged flow velocity variability in the maternal uterine artery from 10–14 to 15–20 weeks of gestation (Table 1). Similarly, a statistically significant decrease ($P = 0.001$) was found for the median LH-ratio during this gestational age period (Table 2).

The graphic presentation of the mean power spectral density distribution in Figure 5 shows a highly concentrated peak in the low-frequency band at 10–14 weeks, whereas at 15–20 weeks the low-frequency peak is reduced by more

than half with a second peak appearing in the high-frequency band around 0.35 Hz.

Comparison between umbilical artery and maternal uterine artery flow velocity derived parameters

Comparison of umbilical artery and maternal uterine artery flow velocity waveforms showed highly significant differences for the heart rate derived parameters at both 10–14 and 15–20 weeks of gestation. Regarding the median LH-ratio for heart rate variability, there was a significant increase from fetus to mother at both 10–14 weeks and 15–20 weeks of gestation (Table 2). The median coefficient of variation and median LH-ratio for time-averaged flow velocity variability were statistically significantly different between the umbilical artery and maternal uterine artery flow velocity waveforms at 10–14 weeks but not at 15–20 weeks of gestation.

DISCUSSION

This study demonstrates that in the early developing fetus prior to 15 weeks of gestation, the low-frequency components of heart rate variability distribution are almost absent. From animal experiments and adult human studies it is known that the low-frequency band is influenced by combined sympathetic and parasympathetic control, whereas the high-frequency band primarily reflects parasympathetic control. Their ratio is thus a reflection of the sympathovagal balance^{4,6–9}. The very small low-frequency components together with a very low LH-ratio strongly suggest almost complete absence of

combined sympathetic and parasympathetic control under 15 weeks of gestation. From 15–20 weeks of gestation, a significant increase in LH-ratio associated with an increase in the mean integrated power of low-frequency components of the heart rate variability frequency distribution was seen. Fetal heart rate variability constituted only a quarter of the heart rate variability of the mother. Nevertheless we hypothesize that the increase in LH-ratio indicates the functional development of the fetal autonomic nervous system during this gestational age period. Parasympathetic innervation may precede the sympathetic system, since various vagal agonists and antagonists have caused the expected pharmacological effects as early as the 8th gestational week¹⁵. It is unlikely, though, that all the basic requirements for an effective autonomic control system, such as the presence of nerves in the heart and great vessels, the ability of the nerve terminals to produce active neurotransmitters, the presence of an effector organ and the existence of functioning receptors in the effector organ, are present in the 15–20-week-old fetus¹⁵.

The frequency distribution of maternal heart rate variability is similar to previous reports on the adult circulation¹⁴, including a respiration peak associated with cyclic variation of intrathoracic pressure, which mechanically perturbs venous return, pulmonary vascular and aortic pressures, and a cyclic variation in heart rate through centrally mediated mechanisms. Furthermore, cyclic variations in arterial blood pressure influence heart rate through the anatomically mediated baroreceptor reflex¹⁴. In a recent study on sheep it was shown that there is attenuation of baroreceptor mediated sympathetic effects on the maternal heart during pregnancy¹⁶. No differences in maternal heart rate variability were found between the two gestational age periods, suggesting that the growing fetus between 10 and 20 weeks of gestation does not influence maternal autonomic state.

Blood flow velocity variability in the umbilical artery is directly influenced by changes in placental perfusion, while variations in uterine arterial blood flow reflects changes in both uterine and placental perfusion. In the placenta, the situation is even more complex since one has to consider both the hemodynamics of the mother as well as of the fetus, and possibly an interaction between the two. These fluctuations in peripheral resistance in turn can perturb both fetal and maternal central blood pressure and, through the baroreceptor reflex, may lead to compensatory variations in heart rate.

In contrast to the fetal heart rate variability distribution, in which the low-frequency component is absent in the early gestational age period, the umbilical blood flow velocity variability distribution showed a low-frequency component throughout the gestational age period of 10–20 weeks. We hypothesize that the fluctuations in the umbilical blood flow velocity are mainly determined by the mother due to the observation that neither the coefficient of variation nor the LH-ratio were significantly different in the two gestational age periods. On the maternal side of the uteroplacental circulation, a strong low-frequency component was present in the uterine blood flow velocity variability distribution during early gestation. In the gestational age period from 15–20 weeks, when trophoblast invasion reduces the resistance

of the uteroplacental system, the uterine flow velocity variability distribution changed significantly and blood flow velocity distributions were statistically similar on both sides of the placenta. Alternatively, the presence of the syncytiotrophoblast and smaller surface area of the immature villous vascular tree may provide an effective barrier attenuating maternal hemodynamic influences.

Although not currently technically feasible, it would be of considerable interest to record both uterine and umbilical blood flow velocities simultaneously. In this case accurate analysis methods could be applied to determine possible cross-correlation and interactions between maternal and fetal hemodynamics. From our data we conclude that the umbilical blood flow velocity variability may be secondary to maternal uterine arterial flow variability rather than due to primary changes in fetal cardiovascular function.

ACKNOWLEDGMENT

This study was supported by National Institute of Health grant P50-HL51498, SCOR in Pediatric Cardiovascular Disease at the University of Rochester, NY, USA.

REFERENCES

- 1 Van Splunder IP, Stijnen T, Wladimiroff JW. Fetal atrioventricular flow-velocity waveforms and their relation to arterial and venous flow-velocity waveforms at 8–20 weeks of gestation. *Circulation* 1996; 94: 1372–8
- 2 Wladimiroff JW, Huisman TW, Stewart PA. Fetal and umbilical flow velocity waveforms between 10 and 16 weeks' gestation: a preliminary study. *Obstet Gynecol* 1991; 78: 812–4
- 3 Ursem NTC, Brinkman HJF, Struijk PC, Hop WCJ, Kempky MH, Clark EB, Keller BB, Wladimiroff JW. Umbilical waveform analysis based on maximum, mean and mode velocity in early human pregnancy. *Ultrasound Med Biol* 1998; 24: 1–7
- 4 Ursem NTC, Struijk PC, Hop WCJ, Clark EB, Keller BB, Wladimiroff JW. Heart rate and flow velocity variability as determined from umbilical Doppler velocimetry at 10–20 weeks of gestation. *Clin Sci* 1998; 95: 539–45
- 5 Ursem NTC, Kempky MH, De Ridder MAJ, Clark EB, Keller BB, Wladimiroff JW. An estimate of fetal autonomic state by spectral analysis of human umbilical artery blood flow velocity. *Cardiovasc Res* 1998; 37: 601–5
- 6 Akselrod S, Gordon D, Uble FA, Shannon DC, Barger RJ. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; 213: 220–2
- 7 Hyndman BW, Kitney RI, Sayers BM. Spontaneous rhythms in physiological control systems. *Nature* 1971; 233: 339–41
- 8 Finley JP, Nugent ST. Periodicities in respiration and heart rate in newborns. *Can J Physiol Pharmacol* 1983; 61: 329–35
- 9 Pomeranz B, Macaulay JB, Caudill MA, Kutz I, Adam D, Gordon D, Kilborn KM, Barger AC, Shannon DC, Cohen TJ, Benson H. Assessment of autonomic function in humans by heart rate spectral analysis. *Am J Physiol* 1985; 248: H151–3
- 10 Malliani A, Pagani M, Lombardi F, Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991; 84: 482–92
- 11 Wladimiroff JW, Seelen JC. Fetal heart action in early pregnancy. Development of fetal vagal function. *Europ J Obstet Gynecol* 1972; 2: 55–63
- 12 Breborowicz G, Moczko J, Dzinowski J. Quantification of the fetal heart rate variability by spectral analysis in growth-retarded fetuses. *Gynecol Obstet Invest* 1988; 26: 188–95

- 13 Kloosterman G. On intrauterine growth. *Int J Obstet Gynaecol* 1970; 8: 895–912
- 14 Akselrod S, Gordon D, Madwed JB, Snidman NC, Shannon DC, Cohen RJ. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol* 1985; 249: H867–75
- 15 Hirsch M, Karin J, Akselrod S. Heart Rate Variability in the Fetus. In: Malik M, Camm JA, eds. *Heart Rate Variability*. Armonk, NY: Futura Publishing Company, 1995, pp. 517–32
- 16 Lumbers ER, Yu ZY. A method for determining baroreflex mediated sympathetic and parasympathetic control of the heart in pregnant and non-pregnant sheep. *J Physiol (Lond)* 1999; 515: 555–66