Development of Fetal Cardiac Intervals throughout 16 to 41 Weeks of Gestation

Faezeh Marzbanrad[1], Yoshitaka Kimura[2], Kiyoe Funamoto[2],
Rika Sugibayashi[2], Miyuki Endo[2], Takuya Ito[2], Marimuthu Palaniswami[1], Ahsan Khandoker[1,3]

[1]The University of Melbourne, Parkville, Australia
[2]Graduate School of Medicine, Tohoku University, Sendai, Japan
[3]Khalifa University, Abu Dhabi, UAE

Abstract

In this paper a new noninvasive method is proposed for automated estimation of fetal cardiac intervals from Doppler Ultrasound (DUS) signal and fetal electrocardiogram (fECG) as a reference. The proposed method is based on a combination of Wavelet analysis and hybrid Support Vector Machines- Hidden Markov Models (SVM/HMM). This method provides automated beat by beat identification of cardiac valves' opening and closing which are used to estimate the fetal cardiac intervals. The range of these intervals in different gestational age from 16 to 41 weeks was evaluated in this study. The correlation between beat to beat intervals was also investigated. Results show a significant negative correlation between Pre-Ejection Period (PEP) and Ventricular Ejection Time (VET) ($r = -0.61, p < 0.0001$), a positive correlation between VET and Systolic Time Interval (STI) ($r = 0.51, p < 0.0001$) and a significant correlation between PEP and Isovolumic Contraction Time (ICT) ($r = 0.67, p < 0.0001$).

1. Introduction

Early identification of fetal risks is a field of increasing interest and significance in most societies. A large body of research has been advocated various fetal assessment techniques to evaluate antepartum fetal risks that may reduce the risk of intrauterine death [1]. One of the main concerns in fetal assessment is the fetal circulation. In particular the evaluation of the heart activity gives useful information about the fetal wellbeing in the antenatal period.

Electromechanical coupling of the heart is a fundamental and clinically significant part of the heart physiology [2]. Opening and closing time of the cardiac valve and the onset of QRS complex of fetal Electrocardiogram (fECG) are used to obtain systolic and diastolic cardiac intervals as electromecanical coupling parameters. These intervals are depicted in figure 1.

Several methods have been proposed for obtaining valve opening and closing times. Using fetal echocardiography, different parts of the heart structure as well as the blood flow through the valves can be evaluated. But it is an expensive and highly specialized technique [3]. There are simpler and less specialized techniques which use the Doppler Ultrasound (DUS) signal [4-8]. However, advanced signal processing is required to provide reliable estimation of cardiac intervals from DUS signal, since valve motions are not recognizable from the raw signal. A number of non-invasive methods have been proposed which apply band pass filter to the DUS signal and use non-invasive abdominal ECG as a reference [5, 8]. Digital narrow band-pass filter was used by Koga et al. to divide the DUS signal into different frequency shift ranges [5]. However the DUS signal is changing overtime depending on the orientation of the fetal heart and the transducer. The transient nature of the DUS signal as well as the wide changes in the signal content and spectral characteristics is shown by Shakespeare et al. in [6]. Therefore other methods such as Short Time Fourier Transform (STFT) and Wavelet analysis are proposed to be applied to the DUS signal to find the valve movements from the high frequency component of the DUS signal [6-7]. In the previous papers the opening and closing of the cardiac valves are recognized manually by observing the DUS component. In our previous paper we proposed to use Hidden Markov Models (HMM) for automated identification of valve timings from the peaks of high frequency DUS signal component. Using this method each peak is recognized as linked to one of the valve motion events or a transitional state which does not correspond to any valve motion. This recognition is based on the probabilistic model of the sequence of events and timings of the peaks [9].

In this paper a new automated method is proposed to find valve motion timings. This method is based on

Wavelet analysis to decompose the DUS signal and hybrid support vector machines- Hidden Markov Models (SVM/HMM) to recognize valve motions automatically. Using this hybrid method the valve motions can be identified based on not only the probabilistic model of the sequence of events and timings of the peaks, but also their amplitude. The hybrid method has applications in speech processing [10] and it has never been used in this application before. Furthermore the changes of the cardiac intervals from the 16th to 41th week of gestation as well as their correlations are evaluated in this study.

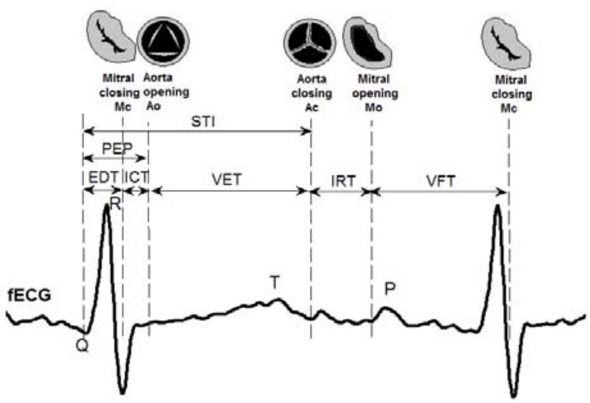

Figure 1 An illustrative example of fetal cardiac intervals: Systolic time interval (STI), Electromechanical Delay Time (EDT), Isovolumic Contraction Time(ICT), Preejection Period (PEP), Ventricular Ejection Time (VET), Isovolumic Relaxation Time (IRT), Ventricular Filling Time (VFT).

2. Methods

2.1. Data

Simultaneous recordings of the abdominal ECG signals and Doppler ultrasound signals from 24 pregnant women with normal single pregnancies at the gestational age of 16 to 41 weeks were collected in Tohoku University Hospital in Japan. A total number of 24 recordings (each of 1 minute length) were sampled at 1 kHz with 16-bit resolution and were divided into three age groups for analysis: 16-28 weeks, 29-35 weeks and 36-41 weeks, including 7, 7 and 10 fetuses, respectively. The study protocol was approved by Tohoku University Institutional Review Board and written informed consent was obtained from all subjects. The continuous DUS data were obtained using Ultrasonic Transducer 5700 (fetal monitor 116, Corometrics Medical Systems Inc.) with 1.15 MHz signals. fECG was extracted from the abdominal ECG using blind source separation with reference (BSSR) as described in an earlier study [11].

2.2. Decomposition of the DUS signal

Wavelet Analysis is the time frequency method to obtain the component of the DUS signal which is linked to the valve motions. It is a powerful technique for analyzing non-stationary signals when their spectral characteristics significantly change over time. By this method, a signal is decomposed into the detailed signals and the approximate signals of the original signal using a set of basis functions.

In this study the complex Gaussian with order 2 was used as mother wavelet. Then the detailed component of the DUS signal at level 2 (100-200 Hz) was taken as the higher frequency content linked to the cardiac valve motions [7]. The absolute value of the detailed signals was obtained and peaks were found from the envelope of the signal based on positive first derivative and negative second derivative criteria. These peaks were linked with the opening and closing time of the cardiac valves.

Fetal ECG was used for segmentation of the detailed signal into cardiac cycles.

2.3. Automated identification of timings by Hybrid SVM-HMM

The Hybrid SVM/HMM method has been developed for the speech recognition [10]. In this study we propose to employ it for the automated recognition of cardiac valve timings from the peaks of the detailed signal. It is a combination of HMM and SVM and more details about HMM and SVM can be found in [12] and [13] respectively. Since HMM is based on probability models, in order to combine SVM and HMM, a probabilistic output of SVM must be obtained. Platt's SVM method [14] was used to provide such an output. In Platt's method the distance of each sample from the separating hyperplane is transformed to the posterior probability of classifying the sample. The posterior probability output of the SVM, $P(class \mid input)$ is obtained by calculating:

$$P(y=+1 \mid f(x)) = \frac{1}{1+\exp(Af(x)+B)} \qquad (1)$$

where $f(x)$ is the classifying function. The parameters A and B are determined by minimizing the negative log likelihood of the training data in the form of a cross-entropy error function. In the hybrid SVM/HMM process the initial probability and transition matrix are first determined based on the HMM training. The SVM is trained based on the training set and classifies the new data in the classes corresponding to the HMM hidden states. The emission probability distribution is obtained from the output of the platt's SVM using the Bayes' rule. Therefore the HMM model is constructed based on which the most probable hidden states are recognized through the decoding process and assigned to the peaks. The states/classes used in this study were the opening (o) and closing (c) of Mitral (M) and Aorta (A), hence four states: Mo, Mc, Ao, Ac; and four transitional states which may occur between the pairs of valve motion events. The transitional states do not correspond to any valve motion. The estimated valve timings were then used with the Q wave of fECG to find the cardiac intervals.

2.4. Statistical analysis

All beat to beat intervals were averaged over all beats for each subject. Then mean and standard error were calculated over the subjects of each age group. ANOVA was used to compare intervals across age groups and Tukey's HSD was used for pairwise comparison.

The correlation of the intervals was also evaluated for all beat to beat intervals for all subjects. Pearson correlation coefficients and P-values were calculated.

3. Results

All 24 subjects were divided into three gestational age groups: Early Gestation (EG) 16-28 weeks, Mid Gestation (MG) 29-35 weeks and Late Gestation (LG) 36-41 weeks, including 7, 7 and 10 fetuses, respectively. For all 24 subjects 100% of R peaks were detected from the extracted fECG and more than 98% of each of the valve motion events was identified across all subjects using the proposed automated technique. An example of identified valve motions for a 37 week fetus is shown in figure 2.

Cardiac intervals were averaged over all beats for each subjects and the mean ± standard error of the averaged intervals across the subjects in three age groups were summarized as in table 1.

Moreover the correlation between the beat by beat intervals was evaluated for all subjects based on Pearson correlation coefficient and P-value. A significant negative correlation was found between beat to beat PEP and VET for every subject. The correlation coefficient varied between $r = -0.6$ and $r = -0.9$ ($p < 0.0001$) across the subjects. Considering all beats from all subjects, the coefficient of correlation between PEP and VET was $r = -0.61$ ($p < 0.0001$). A positive correlation was found between beat to beat STI and VET intervals for all subjects with the Pearson coefficient of $r = 0.4$ to $r = 0.8$ ($p<0.001$). Considering STI and VET of all beats from all subjects the overall correlation coefficient $r = 0.51$ ($p < 0.0001$) was obtained. IRT and STI were also found to be inversely correlated for all subjects with the coefficient $r = -0.3$ and $r = -0.7$ ($p < 0.05$). ICT and PEP were found to be positively correlated for all subjects with the coefficient varying from $r = 0.3$ to $r = 0.9$ ($p < 0.05$) increasing with gestational age (Spearman coefficient: $r = 0.4$, $p < 0.05$). All beat to beat intervals of ICT and PEP from all subjects were found to be correlated with the coefficient $r = 0.67$ ($p<0.0001$).

For other intervals, significant correlations were found for either none or only some of the subjects.

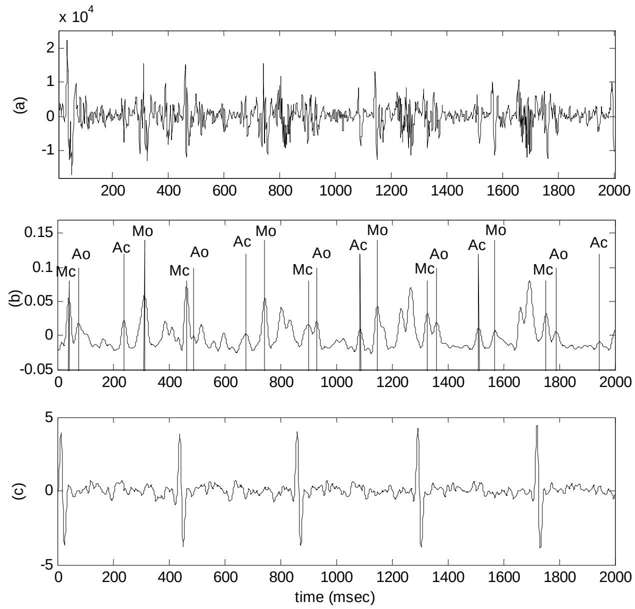

Figure 2 An example of the identified valve timings by the hybrid method. (a) The Doppler Ultrasound signal, (b) The envelope of the normalized absolute value of the detailed signal and the identified events, Mo: Mitral opening, Mc: Mitral closing, Ao: Aorta opening, Ac: Aorta closing. (c) The extracted fECG.

Table 1. Mean ± Standard error (msec) of the cardiac intervals for the subjects of three gestational age groups

Intervals	EG	MG	LG
R-R	393.8 ± 6.7	420.4 ± 25.5	433.3 ± 26.6
EDT	32.3 ± 9.8	38.2 ± 8.1	38.7 ± 8.8
ICT	32.8 ± 1.9	35.9 ± 6.0	37.6 ± 3.3
IRT	70.9 ± 10.3	71.1 ± 16.3	73.6 ± 7.2
STI	224.1 ± 13.7*	239.1 ± 8.5	240.7 ± 12.9*
PEP	65.1 ± 10.6	74.1 ± 12.7	76.2 ± 9.5
VET	159.0 ± 6.8	165.0 ± 13.5	164.4 ± 11.3

* Significant difference (p<0.05) according to Tukey's HSD test

4. Discussion

Slight changes in the mean cardiac intervals were observed by development of the fetus from early to late gestation.

For example an increase in PEP was observed with growing gestation which was also reported in previous studies [8,15]. It was explained with the increase of myocardial mass and the associated prolongation of ventricular depolarization [15].

Further analysis was performed on the correlation of the intervals on a beat to beat basis. Significant inverse correlations were found between PEP and VET for all 24 subjects. It means that when the onset of ventricular ejection is increasingly delayed causing lengthening of PEP, ejection time decreases, therefore STI is not significantly changed. However if VET is prolonged which means the aortic valve closes late after opening, it will also lengthen STI that results in the positive correlation between VET and STI. A positive correlation is also found between ICT and PEP, which was also reported for adult's heart with the coefficient of $r = 0.9$ in [16]. It is also found in an animal study (on dogs) that there is a highly significant linear correlation between PEP and ICT ($r = 0.949$, $p < 0.001$). It has been shown that changes in ICT tend to be followed by a linear change in PEP that is similar in each animal [17].

5. Conclusion

An automated method was proposed to find the fetal valve motion timings from DUS signal and fECG as reference. By using Hybrid SVM-HMM, 98% of the valve motions were recognized from the peaks of the DUS signal component not only based on the sequence of the timing events but also the amplitude and timing of the peaks. The cardiac intervals were estimated based on the fetal valve motions and they were found to be changing with the development of the fetus from early to late gestation. Furthermore some cardiac intervals were found to be correlated with each other on a beat to beat basis.

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Address for correspondence.

Dr Ahsan Khandoker
Dept. of Biomedical Engineering
Khalifa University of Science, Technology and Research (KUSTAR), Abu Dhabi, UAE
ahsan.khandoker@kustar.ac.ae