Electrophysiology in Obstetrics

PhD Thesis

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Content

Introduction

There are few methods available for assessing the well-being of the fetus in utero. Examining the frequency of fetal heart rate: **cardiotocography** (CTG) is essential in daily obstetric practice, however, the sensitivity and specificity of the method should be improved. In case abnormalities are detected on the CTG results, or the amniotic fluid is mecomium stained, the ph value of ***Fetal Blood Sampling (FBS***) may provide further tools for the obstetrician. Since the method is invasive, and the technique is difficult, instead of this sampling, a decision is very often made for a Cesarean section. Additional options are doppler **flowmetry** and **pulse oximetry** for assessing the condition of the fetus; however, the indication scope of these methods is relatively narrow. Pulse oximetry is no longer used in obstetric as a general practice. Over the past two decades there were high expectations in respect of the ***STAN device (ST Analysis of the Fetal ECG during Intrapartum CTG Monitoring***). The device monitors the fetal ECG and the changes in the ST segment during delivery, recorded through direct scalp electrodes. Unfortunately, as this device is expensive to use, and it requires expertise, it is not used broadly. The most recent studies have shown that the use of the STAN device did not result in the decrease of Cesarean sections, and therefore the routine application of the device is not recommended.

In the light of the above it is obvious that there is a significant need for an examination method (methods), which would provide additional information on the well-being of the fetus in utero during pregnancy and delivery. Such method should be cost effective and in this way accessible to a broad range of target public, the use should not require special expertise, and should, above all, improve perinatal morbidity and mortality statistics.

Objective

Our aim is to develop an **electrophysiological measurement system** (hardware and software) and procedure, which combines the possibilities offered by state-of-the-art technology and bioinformatics, and takes advantage of the available resources, and in this way, it is able to:

- provide "true-to-form" fetal ECG (suitable for morphological evaluation) in a non-invasive (indirect) way, through normal Ag/AgCl electrodes (**indirect fetal ECG**).
- record real-time, true-to-form fetal ECG with form accuracy during delivery, through fetal scalp electrode (**direct fetal ECG**).
- record **fetal EEG** (electroencephalogram) through direct fetal scalp electrode. Our goal is to develop a methodology which in real time and continuously provides information on the well-being of the fetus through the analysis of the EEG waves.
- examine the sight and hearing of newborns through the measurement of the triggered brainstem potentials.
- study the micro-potentials of the heart. We would like to create high resolution "clean" ECG signals in a non-invasive way, which show *His potential*s and *After-potentials.*
- objectively examine the contractions of the uterus (*tocometer*).

Our primary objective was to develop a complex electro-physiological system which makes it possible to perform the above examinations, with special emphasis on non-invasive and direct fetal ECG.

Furthermore, our aim is to examine **the short-term effects of smoking on the fetus** in the third trimester of pregnancy, with the use of electrophysiological methods. In our study we seek to answer the question of how smoking affects the cardiac function of the fetus and the mother during pregnancy, and in case it is affected, the change can be detected with the use of electrophysiological methods.

At the time of writing the software, it was expected to have user friendly interface, "high level" signal processing algorithm design, and automated evaluation. Our goal is to provide multi-channel sampling on high sampling frequency, and in this way linking different types of measurements (examining maternal and fetal ECG, fetal EEG and contractions simultaneously).

The importance, the existing methods and the results of fetal ECG

In addition to the assessment of the well-being of the fetus in utero (hypoxia), fetal ECG is suitable for detecting certain congenital heart defects and cardiac conduction disorders. Congenital heart defects (CHD) are among the most common birth abnormalities, considered the leading cause of deaths resulting from birth abnormalities. Each year 1 out of 125 deliveries is affected by some type of (from mild to very severe) congenital heart defect. To this day, the fetal electrocardiogram led from the maternal abdomen has not proved to be sufficiently effective in detecting hypoxia in utero, or any other defects. The reasons for such above mentioned difficulties: the fetal signals are disturbed by several other signals: noises caused by movements, maternal electrical signals, brain activity, etc; not to mention that the fetal signals cross a number of different insulating media with dielectric properties before reaching the body surface.

However, on the basis of direct fECG, there were high expectations in respect of frequency monitoring carried out during delivery as early as in the 1970s. It was expected that the perinatal outcome will improve. Direct fECG-based heart rate monitoring has increased the frequency of Cesarean sections and assisted deliveries (forceps, vacuum) in relation to intermittent auscultation; however, it did not improve statistics on perinatal mortality and morbidity. Nevertheless, in the United States direct fECG-based heart rate monitoring is used during approximately 85% of the deliveries. Direct fetal ECG is primarily used for heart rate examinations, not for analyzing formal deviations in ECG results. The basic reason for this is that the appropriate technology is not available.

Currently, the only commercially available direct fetal ECG detection system worth mentioning is the **STAN device** (STAN monitor, Neoventa Medical, Goteborg, Sweden), which also analyzes the ST segment. The device records more or less true-to-form fetal ECG through the fetal scalp electrode. Obviously, the monitor may be used during delivery and after rupturing the fetal membranes. The STAN device monitors the ratio of the R and T waves of the fetal ECG, and the presence of the biphasic ST segment. The physiological basis for this is, that the repolarisation of the (and not only) fetal heart is very sensitive to hypoxia, during which the elevation of the ST segment and the T wave is detected.

At the same time with our development, the **Monica AN24** device was released, which records non-invasive fetal ECG, but it is only used for determining the heart rate, and not for the examination of the formal variations.

Method and patients

The obstetric examination device developed by us is a complex electrophysiological measuring system which consists of a special hardware (Dr. Lóránd Kellényi) and the software developed for it (Dr. István Péterfi). The device is suitable for performing a number of electrophysiological examinations, such as: 1. non-invasive fetal ECG (indirect fetal ECG during the third trimester of pregnancy), 2. recording fetal ECG during labour through direct lead, i.e. through fetal scalp electrode, 3. real-time fetal EEG monitoring during labour, 4. monitoring contractions of the uterine muscles, and fetal movements. In addition to the mentioned and planned mayor examinations, our system is suitable for testing newborn sight and hearing, but it is useful for advanced cardiac and neurological analysis as well.

The examinations were performed with the permission of the **Ethics and Research Ethics Committee of the Kaposi Mór Teaching Hospital, Somogy County.** (License: 6 February 2012, renewed license: File no. IG/00467-000/2017)

This research was primarily aimed at developing a new biological measuring system and methodology, instead of performing statistical tests established for the medical science. Therefore, there is no group of patients classifiable on the basis of well-controlled conditions.

Pregnant women in the second and third trimester of their pregnancy volunteered to take part in our development work, who signed their written consent following appropriate information.

Results

Non-invasive (indirect) fetal ECG

While the maternal ECG shows an amplitude of about 1mV, the amplitude of the fetal ECG R waves measured through the abdominal wall rarely exceed the value of 30-40µV. This signal of 25-50x smaller voltage may not be registered by the normal ECG device. The signal strength of fetal ECG corresponds to the normal signal level of EEG, but the frequency range of 30-75 Hz should be increased at least to 1000Hz.

Depending on the position of the fetus in utero, the distribution of the maternal body surface potentials varies. When registering a non-invasive fetal ECG, an ultrasound examination should be performed for information purposes, in order to place the electrodes in the most suitable locations. If several electrodes are placed, more leads may be applied for the pairs.

During recording transabdominal fetal ECG it is a serious difficulty that - in addition to the useful fetal signal - the maternal ECG is also present, with a much larger amplitude. In this case the maternal signals are considered noise, however, unlike the concept of classic noise, the morphology of these waveforms is nearly constant, and they are cyclically recurring. The first step of retrieving abdominal fECG is clearing the abdominal recording from the interference of maternal ECG waves. In order to achieve this, an algorithm should be prepared, which recognizes the maternal signals. (generally accepted are maternal ECG R waves, and the algorithm used widely, the **Pan-Tompkins QRS detector)**

Our system is designed to be capable to generate a **"start/trigger" signal** not only from ECG, but other types of electrophysiological signals as well (EEG, EEM, BERA, etc.) During electrophysiological measurements, the trigger signal's role is to average the "useful events" accurately, in the phase. A special peak detecting algorithm has been designed, which detects the trigger events regardless of the direction of the detour, in this case the maternal ECG R wave, and on such basis prepares the average of the maternal ECG curve after a few cycles. After this - in real time - our algorithm subtracts the previously created average from the detected maternal heart cycles, in this way cleaning the abdominal recording from the interfering maternal signals. Using the same peak detection algorithm for the "cleaned" recording, now we detect the fetal ECG R wave, and prepare the average of the fetal heart event.

During the recording of non-invasive fetal ECG we are sometimes faced with the fact that the fetal signal detected through the maternal abdomen is so weak that it is completely suppressed by the noise, and its location can't even be recognized visually. There is a more common case, when the fetal sign is visible, however, it is still "invisible" for our peak detecting algorithm. We came up with an innovative idea and were able to successfully trigger a start signal from the acoustic signal of a CTG device.

After level adjustment and double rectification, the acoustic frequency signal output of the ultrasound device was totalled and integrated. The envelope curve of the integrated signal can be used to generate a trigger signal.

Recording direct fetal ECG

Special, commercially available fetal scalp electrode is used for sampling. In the intrapartum period when the status of the cervix (dilated at least 2 cm) allows, or there was artificial or spontaneous rupture of the membranes, the fetal scalp electrode can be attached. Our system, similar to the indirect method - but this time only in one channel - performs the sampling at 5KHz sampling frequency. After automatically identifying the fetal ECG R waves, it prepares the average of the heart events, the true-to-form fetal ECG, which is displayed on the **averaging panel**. The true-to-form fetal ECG can be enlarged optionally or is suitable for performing various measurements. In addition, the program also prepares the usual CTG curve on the **CTG panel**, and the true-to-form fetal ECG can be examined separately for each heart rate domain. If required, the CTG panel is suitable for displaying the maternal ECG frequency registered at the same time.

Direct fetal electroencephalography (fEEG)

Several studies have reported that hypoxia causes a change in the EEG pattern and frequency spectrum. Hypoxia reduced the lower EEG frequencies, while re-oxygenisation increased the higher EEG frequencies.

Fetal EEG is registered with the use of the specially modified version of the scalp electrode mentioned in the previous chapter. Not one, but two "spikes" are needed at a standardized distance of 2cm apart. The voltage between the two electrodes is recorded (EEG). Since the fetal scalp area - where the electrode can be attached - may not be standardized (the electrodes can always be placed on the front part), instead of examining the formal changes of the EEG curve, the frequency spectrum of the few-second-long sections should be examined, which is automatically prepared by our program and displayed on the EEG panel in the form of a colour map.

Non-invasive measurement of His and other micropotentials in adults

The high sensitivity of our biological measurement system, the sampling frequency ranging from analogue 0.1 Hz to 3,000 Hz, the hardware-produced outstanding signal to noise ratio, and the possibility of telemetry signal transmission inspired us to test our system with other disciplines as well. Unlike the images created with traditional ECG equipment, our objective was to create a high-resolution ECG recording

of adult heart activity - in a non-invasive way, through traditional leads - which also makes it possible to visualize micropotentials. Such micropotentials are e.g. bundle of His activity, or After-potentials, which are associated with sudden cardiac death. During breathing, the heart that lies on the diaphragm, follows its movement, so the heart's electrical axis "waggles". The electrical axis of the depolarization of the His bundle with very small potential is also modified by the movement of the heart. When looking at it from the static lead, it is shown that when the heart events on the same phase are averaged, they have a dampening effect on each other due to the waggling of the electrical axis. The heart events are synchronized to breathing, therefore, events with the same field orientation can be averaged.

Our system was also tested at Heart Institute of the University of Pécs during invasive cardiac catheterization intervention. Our non-invasive, telemetry measurement perfectly correlated with the invasive measurements.

The direct effect of smoking on fetal ECG

We examined the direct effect of smoking on fetal heart functions in the third trimester of pregnancy, in the smoking pregnant women, adapted to their smoking habits. Fetal ECG was recorded before, during and after smoking. During the examinations "bit to bit" analysis was performed. The fetal heart rate per minute was calculated from the successive fetal R waves, and the frequency was presented in histograms. During smoking the dominant frequency is increased compared to the previous state (the basic frequency increases). This increase is of minimum value in the case of intense smokers, while it is significant in the case of occasional smokers.

One of the major results of our study is derived from the secondary derivative of fetal heart events (R-R' analysis), which is simply the change in successive fetal heart rates (short-term variability). During smoking, fetal short-term variability is significantly narrowed, which is a clear indication of fetal stress. Interestingly, when fetal stress was apparent, we often found that the short-term variability of maternal heart rate widened, indicating the mother's relaxation, tranquillity and "well-being".

Not surprisingly - we found no signs of ischemic condition in the fetal ECG during smoking. The fetus is also "prepared" for much greater stress, therefore one or two cigarettes are not likely to cause permanent damage. However, in several cases we noticed that a few minutes after the start of smoking, when the fetal heart rate increases, the morphology of the T wave changes, and then, at the elevated "peak"

section, it becomes similar to the initial form. The reason for this is probably a fetal compensation process, which requires further research.

Discussion

The electrophysiological system (hardware and software) we developed may be used in several physiological areas where the gained electrical signal is so small that it cannot be detected by the conventionally used, or commercially available devices. Such areas include: fetal ECG, fetal EEG, leads of His bundle potential and micropotentials in adult ECG, as well as neonatal hearing and sight tests. The PhD thesis primarily summarizes the results and perspectives from the fetal ECG recordings, using our technology under development. Although it has its limits, but direct fetal ECG measured during birth with direct fetal scalp electrode is already available (Stan method). However, recording fetal ECG during pregnancy through the mother's abdominal wall (indirect fetal ECG) is not solved on international level. At almost the same time with our development, the Monica AN24 device was released, which records non-invasive fetal ECG, but unlike our system, it is primarily used for determining the heart rate, and not for recording true-to-form fetal ECG.

With our system we are able to create true-to-form fetal ECG in 80% of the cases in the third trimester of pregnancy, using the method of leads from the maternal abdomen. The use of the device does not require highly trained personnel. The relatively low cost would allow for widespread use. The use of the module as a routine screening test could result in detecting a larger percentage of congenital heart defects, since, as it was described above, a substantial part of congenital heart defects is shown as deviation on ECG. Today, during routine screening tests, only half of the congenital heart defects are detected. In case prior to an ultrasound test it would be possible to perform a non-invasive fetal ECG, the ultrasound examination could be carried out for the "suspect" cases with focused attention - and perhaps at specialized centres. In addition to detecting congenital heart defects, indirect fetal ECG during pregnancy is even more important for detecting intrauterine hypoxia and placental insufficiency, primarily in case of pathological pregnancies (hypertension, praeeclampsia, diabetes, intrauterine fetal retardation).

On the basis of data from literature, 10-15% of cases of central nervous system damage caused by intrauterine hypoxia are formed before birth. Therefore, evaluating the status of the fetus in utero is of great importance in the second and third trimester of pregnancy. Methods currently used in obstetric practice (non-stress

test, oxytocin stress test, Doppler ultrasound flowmetry) are not sufficiently predictive, false positive and false negative results are common. The objective examination of indirect fetal ECG, primarily the objective examination of the ST segment could provide warning earlier for any emergencies.

On the basis of the above, and despite the difficulties reported in literature, we have managed to introduce our achievement, the use of indirect fetal ECG, into practice during the ECG examination of the fetus of smoking pregnant women. During our measurements we have observed that a distinction must be made between heavy smokers (more than 10 cigarettes per day) and occasional smokers. In the case of the latter, the measured deviance is greater than in the case of heavy smokers. The reason for this is probably a fetal compensation process, the mechanism of which requires further research.

The effect of nicotine on the ECG of adults was previously examined. According to the study, it does not change the heart rate, and does not cause ischemic conditions, either. The increase in the basic frequency of fetal heart rate during smoking may possibly be connected to hypoxia. There were previous studies using electrophysiological methods aimed at the direct effect of smoking on fetal heart. The test was primarily based on heart rate variability analysis. Their results support our results: during smoking both the short and the long-term variability is changed. The changes are reversible, and the deviations shown are similar to the ones in abnormal cardiovascular conditions in adults. No data was found in scientific literature on studying formal changes in fetal ECG during smoking.

It can be concluded that smoking has a direct effect on the fetus, on fetal cardiac function, which can be demonstrated by electrophysiological methods. The change is primarily reflected in the variability of fetal heart rate and is characterized by patterns similar to stress in adults. In this way we have demonstrated that the fetus is exposed to stress during smoking. In addition to the long-term effects, the short-term adverse effects may be justified as well.

During parturition, after the rupture of the membranes, our fetal ECG device performing the recordings from the direct lead of the fetal scalp electrode not only reaches the performance of the STAN device, but it could also exceed it with the development - using telemetry - of the system. The STAN device monitors anomalies compared to the level of the initial ST segment, and generates a warning STAN event. In this way, if the fetus is already hypoxic, the abnormal ST segment is considered normal, and there is no warning for anomalies. Our system is able to

separate averaged fetal ECG into its elements; therefore, it would compare the ST segment to the level of PR segment considered isoelectric.

Among the additional uses of our electrophysiological system, probably the most substantial area - although the basics of which have hardly been researched - is fetal EEG examined with scalp electrodes during labor. The examination of direct fetal EEG during labor has huge perspectives, as exactly that organ (brain) can be directly and continuously observed which most likely determines the overall quality of life. The method - ECG lead - has been used successfully; however, the development of EEG curve evaluation requires further work. It would be worth comparing the results obtained from the EEG with the pH of the blood taken directly from the fetal scalp, and with the results obtained from the CTG curve, and the ultrasound flowmetry tests.
The ultimate objective is to improve the indicators of perinatal mortality and morbidity. Our newly developed electrophysiological method actually works; its importance will be more accurately assessed after a large number of use in testing pathological pregnancies and following comparison with other methods assessing fetal intrauterine conditions. By all means, our examination in respect of recording fetal ECG during pregnancy can be considered a cutting-edge research in the world.

New findings and results

Building on the basics - using the opportunities offered by technology and the enormous resources provided by bioinformatics - we were able to develop a hardware and a software that enables the recording of true-to-form fetal ECG - in the third trimester of pregnancy - through the mother's abdominal wall in 80% of the cases.

The biological amplifier we have developed makes high-frequency sampling possible, while ambient noise level is kept to a minimum. Telemetry and opto-electrical signal transmission is also used.

We have developed new signal processing algorithms in our software. We have developed a new method for the filtering of the maternal signals - causing interference in our case - and created a new peak detector algorithm. A unique solution enabled us to automatically break down the biological signals into their components.

We managed to use the Doppler signals of cardiotocograph (CTG) for synchronizing fetal heart events.

Smoking pregnant mothers were tested with our system, and it could be confirmed that smoking has a direct impact on fetal ECG; in particular the fetal heart rate variability is changed, and a pattern similar to the heart of adults in stress. Smoking also changes the fetal ECG T wave morphology.

With our system we could also indirectly examine in adults the micropotentials of the heart, such as the His potential or the After-potentials. The After-potentials have direct role in sudden cardiac death; therefore, it is of great importance that this information may be available during out-patient tests.

From direct leads (through fetal scalp electrode) we are able to produce fetal ECG in real time, in very good resolution. Our system can also support Stan devices.

We have developed a new method for the real-time recording of fetal EEG during labor, which method is still absolutely unique in the world. The integrity of the central nervous system of the fetus can be monitored in real time.

Finally, our system is suitable for examining the sight and hearing of newborns through the measurement of the triggered brainstem potentials.

"Electrophysiology in Obstetrics" lectures

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