Redefining fetal evoked fields with biomagnetic recordings over the whole maternal abdomen

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Abstract- **The development of a technique for the recording of fetal brain activity has been highly limited by the inaccessibility of the developing human brain in utero. Based on the needs of resolution and a non-invasive nature, only biomagnetic measurements are suitable for the determination of the integrity of the fetal brain on a routine basis. We have built a new biomagnetic measurement device dedicated this task. The main construction concerns were those of patient comfort, ease of performance of standard measurements, and appropriate spatial and temporal resolution. Our initial evaluation of the instrument has shown that it is capable of obtaining signals traditionally regarded as evoked fetal fields. Our results also show that this interpretation has to be made very carefully and that a large scale array is more appropriate for the extraction of fetal brain signals.**

***Keywords*- fetal magnetoencephalography, auditory evoked fields (AEF)**

I. Introduction

Since the first publication of fetal auditory evoked fields (fAEF) [1] only a small group of researchers have been attracted by this procedure. This is mainly due to the low signal to noise ratio of the fAEFs, which makes it difficult to record the fAEF reliable and until now it was reported that up to 50% of patients in the third trimester showed fAEF [2-4]. Most studies (including our preliminary study) were performed with limited spatial resolution of the sensor array and the results were judged mainly on visual inspection and restriction to the search of a presumable evoked field around a latency of 200 ms. This latency restriction was based on newborn recordings showing a peak at around 200ms for standard auditory evoked potential recordings performed with electrencephalography (EEG). The missing of a component structure compatible with the newborn EEG (consisting of several distinguishable components, the largest are around 100ms and 200ms) was not discussed in detail and possible interpretations of the fetal MEG recordings were related to an increased delay or simply inaccessibility of certain components. The reported signal strengths were highly variable and ranged between 50 and 150fT In a recent paper much lower signal strength was reported, but it was argued that the signal to noise was increased by using a more sensitive system [5]. The specific problem in the recording of fAEF is the elimination of the main contributing signal sources to the measured signal, the maternal and fetal heart.

A tone burst of a certain frequency, is commonly used for recording fAEFs. The studies published until now used a tone frequency above 1kHz. Based on the fact that the sound has to be delivered to the fetus through the abdominal wall it is very important to take into account the attenuation properties of the abdominal wall to sound stimuli. Animal and human studies showed that the attenuation coefficient is highly frequency dependent. Best transmission can be achieved in the frequency range below 1kHz, for higher frequencies the sound is highly damped [6]. This has to be taken into account in the discussion of the currently available results.

Long latency auditory recordings of preterm and term newborns with electroencephalography, have shown that the reliability of identifying various components of long latency evoked potentials is between 50 and 75%. [7]. This implies that acoustic stimulation in the fetus has to be carefully planned to gain a high enough reliability to use fAEF for developmental studies and extend this studies for a clinical setting.

There are also other approaches for eliciting auditory evoked responses, that are based on the mismatch negativity (MMN). This component appears as a negative peak in electroencephalographic recordings, if the difference wave of the evoked potentials generated to rare and common stimuli is calculated. This component is a related to preconscious sound discrimination and is regarded as one of the earliest discriminative fetal response based [8]. For preterm and term newborns it was shown that the MMN was observable in a latency range between 300 and 500 ms [9].

II. Methodology

Recordings were performed with a newly developed device – SARA (SQUID Array for Reproductive Assesment, CTF Systems, Inc. Vancouver) [10]. The SARA system has a 151-SQUID primary sensor array curved to fit the shape of the maternal abdomen. In addition, there are 29 reference SQUID sensors which are used to reduce the environmental magnetic noise and artifacts due to mechanical vibration that may be coupled to the system. The primary sensors are first order gradiometers with a baselength of 8cm, the reference channels are first order gradiometers and magnetometers. The reference channels can be used to eliminate external noise and generate software based higher order

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Abstract

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gradiometers. The overall white noise levels of the SARA are below 5 fT/Hz$^{1/2}$ and the bit resolution of the sensors is 0.3 fT/bit. The SARA system is installed in a magnetic shielded room (AK3-Vakkuumschmelze, Germany). The pregnant mother sits on a saddle like chair and leans against the sensitive part of the array (Fig. 1). During the study the mother is instructed to stay as still as possible. Before the study, outside of the shielded room, the position of the baby is determined with an ultrasound and recorded for further comparison. The stimulation device consists of a speaker, placed outside the shielded room, attached to a 20 feet long piece of Tygon tubing. The other end of this tubing attached to a respiratory mask. This mask is secured with a belt and attached to the back of the mother and is oriented to point to the fetal head (Fig. 2). The sound intensity was measured in the air, both at the end of the mask (120dB) and in the shielded room (100 dB) This means our sound delivery generates a focussed sound source and a diffuse sound source. The stimulus is a 100ms tone burst with a frequency of 1KHz and rise and fall times of 10ms. The mean interstimulus interval is 2s with a randomisation of 100ms.

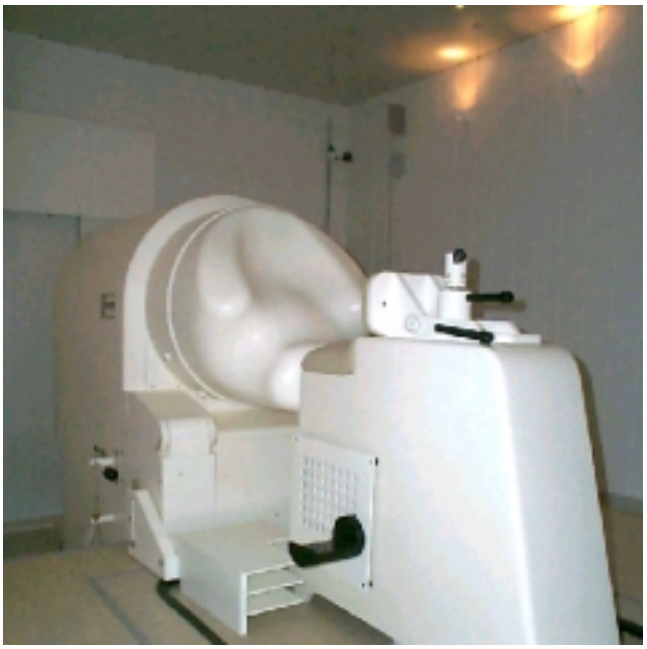

Fig. 1. The SARA system including the adjustable dewar and the patient support system.

This study is approved by the Institutional Review Board (IRB) and informed consents were obtained from the participating mothers. The recording sessions consisted of 6 trials each, 2 minutes in a continuous mode at a sampling rate of 312.5 Hz and an antialiasing filter of 100Hz. In addition a the sound delivery times were recorded on a trigger channel. After recording, the datasets were inspected for gross movement of the mother and the fetus, and these trials were disregarded from further analysis.

The long trial data were segmented in relation to the trigger with 200 ms pretrigger time, for baseline, and 1000 ms posttrigger time. A coherence based algorithm [11]was used to eliminate the influence of maternal heart signals using 30 channels in the upper part of the sensor array as references to the maternal heart. The field distribution after the maternal heart signal removal were visually inspected for evoked potentials.

We used a new stimulation protocol called the auditory mismatch paradigm on two fetuses. This protocol consisted of 300 stimuli of which 80 % were 500 Hz tone and 20% were 1kHz tone. The tone burst length was 100 ms and the rise and fall time was 10 ms. In addition we recorded simultaneously maternal electrocardiogram (ECG, leads I, II, III and V2) with MEG compatible electrodes. The ECG signal was synchronized with the MEG recording, by feeding them through analog-to-digital (A/D) channels in the MEG electronics. In this analysis, the coherence algorithm used the ECG signals as references to remove maternal heart interference.

For further studies we also developed a three dimensional localization system to correlate physiological signals with anatomical information. Every recording on the SQUID device is performed with three localizations coils attached to the left and right belly and at the spine. This coils are activated before and after every run and the position of the coils is determined in relation to the sensor array. Before the MEG measurement, three dimensional localization sensors are attached to the mother at the same position as they are used during the MEG. With a free-hand three dimensional ultrasound system (3D Echotech, Germany) a 3D image of the heart and the head is recorded. Before and after the measurement the position of the localization coils is determined and during the recording the position of the scan head is recorded. This information is used to generate a transformation vector and a rotation matrix which determines the position of the 3D picture in space. The recording program was developed by 3D Echotech, the post processing programs are developed by our group.

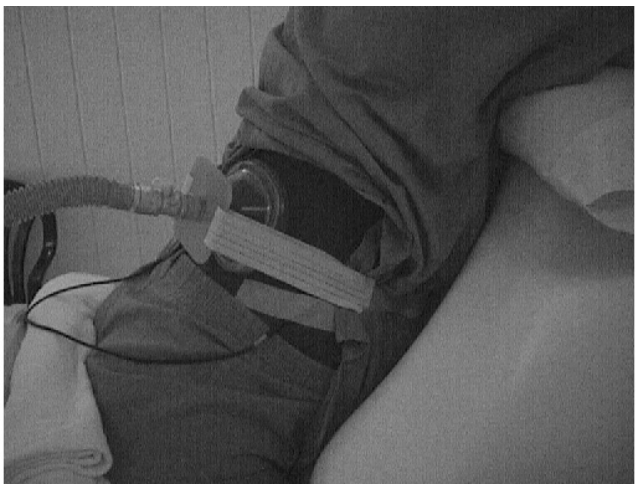

Fig. 2. A pregnant patient sitting on the SARA device. The auditory stimulation device and the localization coils are attached to the patient.

III. Results

The coherence algorithm was able to remove the maternal heart signal in all cases. Based on our analysis method and provided that the region of interest (ROI) is restricted to a small area above the fetal head, we were able to identify in 14 out of 22 fetuses signals which resemble the reported fetal evoked responses. A typical example is shown in Fig. 3. and includes phase reversal on certain channels and a peak around 210 ms. In addition our signal to noise ratio is similar like the one reported recently [5]. The latency and field strength for all 14 fetuses is given in Tab 1. Fig. 3a shows the time course of all array channels and the enlarged time courses from the ROI are shown in Fig. 3b. It is obvious, that the examination of signals only within a small area ROI can lead to an impression that there might be a fetal signal, including phase reversal. However, when the signal distribution over a larger area is examined, it is seen that what on the basis of small ROI was thought to be a fetal signal, is in fact only a small part of a large scale field fluctuations. Example in Fig. 3 illustrates that if the ROI is selected too small, the real signal extrema can be missed and their position could be mistakenly placed at the rims of the ROI. Since the fMEG detection geometry can be crudely approximated by a seminfinite plane, one can use a consistency check based on the "rule of thumb" for the distance between the two field extrema [12]. As an example, consider e.g., the fetal head depth of 4 cm, vacuum gap in the dewar 1.5 cm, and the source depth in the fetal head 0.5 cm. Then the source depth below the sensors would be about 6 cm and the expected separation between the field extrema should be about 8.5 cm. In addition, if the fetal head was assumed to be electrically isolated from the maternal abdomen, the fetal signals would not need to exhibit conventional dipolar patterns (the signals could be monopolar or highly asymmetric bipolar). In addition split time averages over the first, second and third 100 stimuli, made it difficult to define the evoked fields seen in the average.

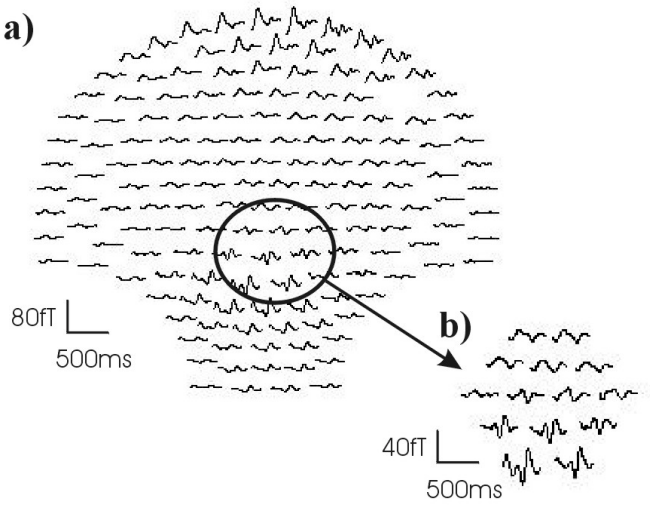

Fig. 3. Averaged auditory evoked fields for the 151 channel array related to tone bursts. a) Distribution of the primary sensors and the corresponding MEG traces. The region of interest is marked with a circle around the sensors. It is evident that the evoked field in the region of interest is mainly dominated by maternal interference, which is small for the sensors in the region of interest, but could be interpreted as evoked field. b) Field distribution in the region of interest, a clear evoked field is visible, which shows in addition phase reversal.

In the preliminary study with the mismatch paradigm, we got a difference wave form for the mismatch activity including an initial deflection around 150 ms and a activation around 300-500ms. In addition spatial filter techniques showed a normal component structure. The use of spatial filters is highly depending on the capability to provide anatomical information about the fetus in a common reference frame of MEG and ultrasound. Our initial tests with the localization coils showed that the coregistration error is in normal cases below 1cm.

TABLE 1
SUMMARY OF FETAL AUDITORY EVOKED FIELD MEASUREMENT[a]

patient number	gestational age (week)	strength (fT)	latency (ms)
30	30	25,2	170
34	32	41,4	224
19	36	15,3	253
28	36	11,6	265
29	37	21,4	246
32	37	7,3	221
33	37	6,7	192
44	37	15,1	180
45	37	6,3	215
23	38	32,6	270
38	38	6,3	243
27	39	11,4	192
50	39	15,5	180
39	39	13,1	202
40	40	11,2	237

[a]The latency and amplitude is given for the largest component

IV. Discussion

Our results indicate that any fAEF signals must be carefully interpreted and subjected to a battery of tests to assure that they are real. We think that the identification of fAEF can not be made solely on the basis of the topology, a peak in the expected time range and a limited ROI. Because the maternal and fetal heart interference is about 100-1000 times larger than the reported fAEFs, it is necessary to take

into account the overall field distribution. This is only possible by recording the activity over the whole maternal abdomen in one trial. For this analysis we did not eliminate the fetal heart signals by a filter approach, because the small distance between fetal heart and fetal brain could lead to the elimination of the fetal brain signal or to a spurious signal by non appropriate filter design. In addition one has to show that other effects cannot reproduce the same field distribution. For example, it is not known what effect the stimulation can have on other biological process like the fetal heart and eye blinks.

V. Conclusion

In future it will be necessary to develop more controlled protocols by combining fetal behavioural tests and fAEF recordings, to generate convincing evidence that reported fAEF are generated in the fetal brain. New analysis techniques based on various spatial methods should be used to identify locations where the fetal brain signals are generated. This can be achieved by the coregistration of 3D ultrasound and MEG.

In addition we hope that more elaborated protocols are used in this field, which show the competence of the fetus in relation to its discriminative capabilities, which can have more clinical applications. The approach by a whole abdominal recording in combination with anatomical information seems to be the only reliable approach for recording fetal evoked fields and hopefully, after a better characterization of fetal and maternal biomagnetic sources we are able to extract spontaneous fetal brain activity and reliable evoked fields.

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