Neonatal magnetoencephalography and spectral analysis

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Summary

Purpose: We performed a prospective study of neonatal brain function on 44 respective term neonates who were delivered normally, without any clinical signs of brain damage. Thirty were associated with a normal pregnancy and labor with normal values of Apgar scores, umbilical cord pH and birth weight, while 14 neonates were the result of pre-eclamptic pregnancy.

Methods-Results: Biomagnetic measurements were performed by means of a Superconducting Quantum Interference Device (SQUID) in an electrically shielded room of low magnetic noise. Biomagnetic signals (waveforms) recorded from neonatal brains in the frequency range of 2-7 Hz were expressed in terms of magnetic power spectral amplitudes. These were low (mean value 163.2, SD 22.57) in almost all neonates from the "normal pregnancy" group, while they were high (mean value 211.6, SD 37.74) in most neonates from the "pre-eclamptic" group. The difference between the two groups was statistically significant (Student's t-test, $p < 0.005$).

Conclusion: A statistically significant difference in spectral amplitudes of neonatal brain activity was observed between normal term neonates and the pre-eclamptic neonates. Biomagnetic measurements of neonatal brain activity could provide clinical practice with a promising procedure for assessing brain function.

Key words: Neonatal brain; Biomagnetic measurements; Normal pregnancy; Pre-eclampsia; Perinatal asphyxia.

Introduction

In recent years there has been a growing body of evidence from laboratory and clinical studies that at least 2% of newborns have been exposed to an asphyxial insult during labor and delivery which may affect their outcome [1]. Despite all the progress achieved in obstetric and neonatal care, intrapartum fetal asphyxia, a condition of impaired blood gas exchange leading to progressive hypoxemia and hypercapnia with significant metabolic acidosis, is still a major cause of hypoxic-ischaemic brain injury in term newborns. Early assessment of the degree of the resulting hypoxic-ischaemic encephalopathy (HIE) is essential for the clinical management and is considered a prognostic factor for the newborn's neurodevelopmental outcome. Pre-eclampsia is a complication of pregnancy that can cause birth asphyxia at or near term, due to the influence on uteroplacental circulation, resulting in brain damage [1-3].

Conventional neurological examination does not provide specific information about the neonate's neurological status as clinical signs of HIE may have a latency time of even 12 hours after birth [2]. Moreover, perinatal variables such as Apgar score and umbilical cord pH have not been strongly correlated with a poor prognosis [4].

Electroencephalography (EEG), ultrasound examination (including Doppler flow velocity measurements and two dimensional imaging), computed tomography (CT) and magnetic resonance imaging (MRI) have been widely applied in high risk infants for prognostic purposes, but they are time and money consuming, and they need experienced personnel for interpretation of the results [5-12]. Moreover, newly developed techniques such as amplitude-integrated electroencephalography (a-EEG) or cerebral function monitoring (CMF), visual evoked potentials (VEP) and near infrared spectroscopy (NIRS) are of promising prognostic value, but they are still under research [2, 13-15].

Recently, magnetoencephalography (MEG) has been investigated as an alternative method for assessing brain function in adults [16-18] as well as in fetuses [19-22].

MEG is potentially an ideal technology because it directly records the extremely weak magnetic fields associated with electrical activity of cortical and subcortical neuronal groups, has high temporal and spatial resolution and is completely safe and non-invasive, since the instrument used acts as a receiver and not as a transmitter [19, 20, 22].

Very few studies in the literature refer to biomagnetic recordings of the neonatal brain [19, 20].

The aim of the present study was to report our preliminary data of MEG recordings on neonates without clinical or laboratory signs of perinatal asphyxia, as well as on neonates who underwent a pre-eclamptic pregnancy, even though they did not have neurological signs of affected brain function. Further improvement of the equipment used, so as to be applicable at the bedside, as well as the method's performance on neonates with brain damage, could probably demonstrate the method to be a promising diagnostic tool for neonatal brain dysfunction.

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Materials and Methods

We performed a prospective study on 44 neonates who were delivered normally between 37-41 weeks of gestation with birth weights between 2150 and 4100 kg. Maternal age ranged from 16 to 39 years. Thirty neonates had a clinically uncomplicated gestation and labor while 14 were associated with pregnancies complicated by pre-eclampsia. All participants met the following criteria: a) gestational age >37 weeks b) normal delivery and c) no clinical sign of HIE on neurologic examination. All neonates with a history of prematurity, neonatal seizures, sepsis, neoplasms, major congenital anomalies of the central nervous system, inborn errors of metabolism or a neurodegenerative disease were excluded from the study. Pre-eclamptic neonates were all delivered over a 3-yr period (1997-2000) meeting the above-mentioned criteria, while "normal" neonates were randomly selected among neonates delivered in the same time period.

The data collected included birth weight, Apgar score, cord pH, gestational age and indications of pre-eclampsia (blood pressure, proteinuria and edema) and MEG measurements. The criteria of diagnosing pre-eclampsia were those defined by the American College of Obstetricians and Gynecologists (1986): a blood pressure of 140/90 mmHg or higher on two separate measurements 24 hours apart, with proteinuria or edema or both, in the absence of any underlying chronic renal or vascular disease [23]. Biomagnetic recordings were obtained between 24 and 72 hours after birth, since measurements do not present significant differences in such a short interval, as Wakai [20] demonstrated. Informed consent to examine each newborn was requested from either parent. The Hospital's Ethics Committee approved the entire examination procedure.

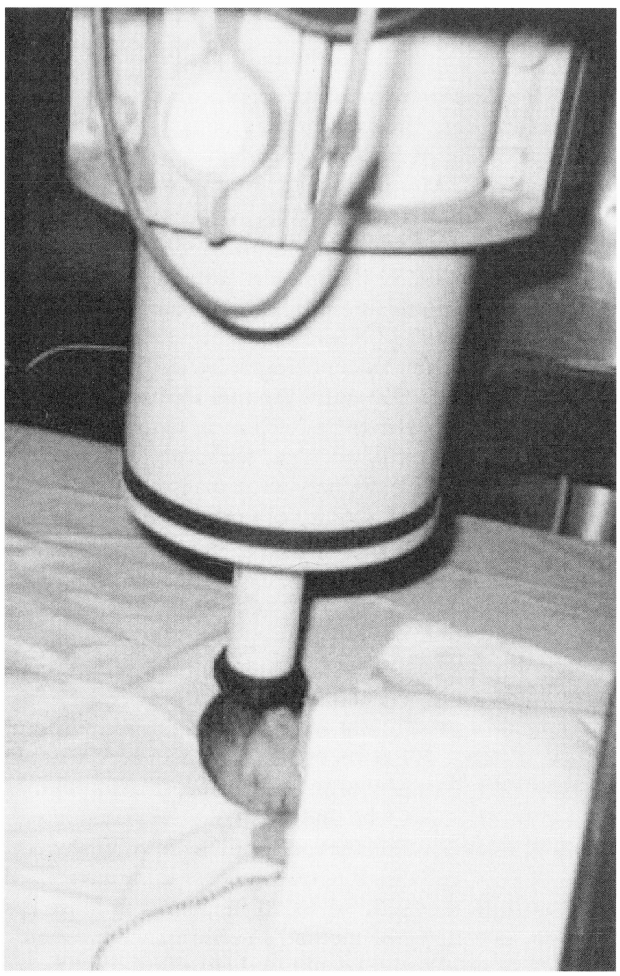

Figure 1. — The SQUID and the neonate during MEG measurement.

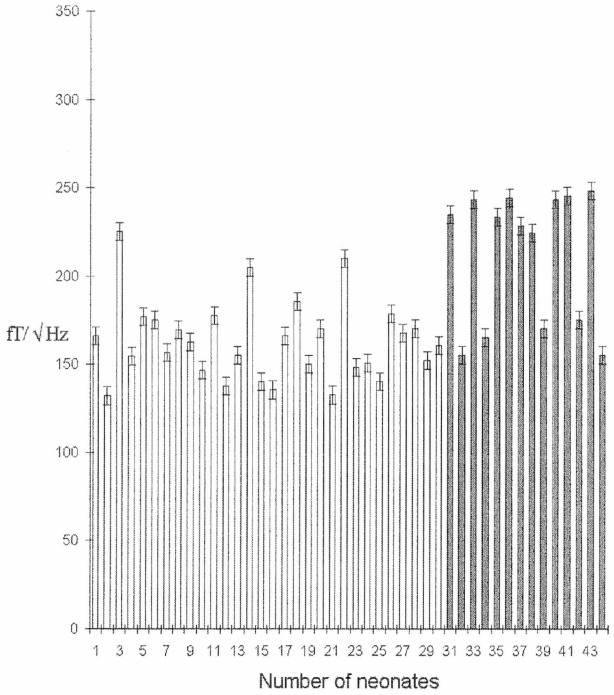

Figure 2. — MEG measurements from all neonates included in the study.

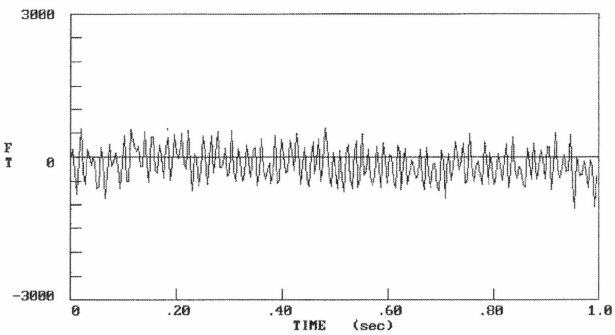

Figure 3. — Neonatal brain MEG measurements following a normal pregnancy.

Biomagnetic recordings were acquired using a commercial one-channel SQUID (Superconducting Quantum Interference Device – DC SQUID, model 601, second order gradiometer, Biomagnetic Technologies), of high sensitivity (95 pTesla/Volt at 1000 Hz). To prevent interference from external electromagnetic fields, the system

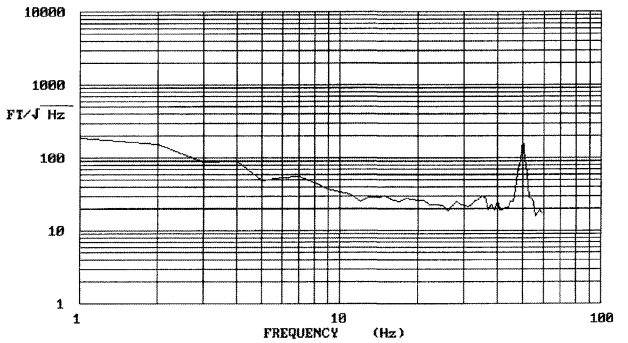

Figure 4. — The spectral amplitudes of the waveforms shown in Figure 3 after statistical Fourier analysis

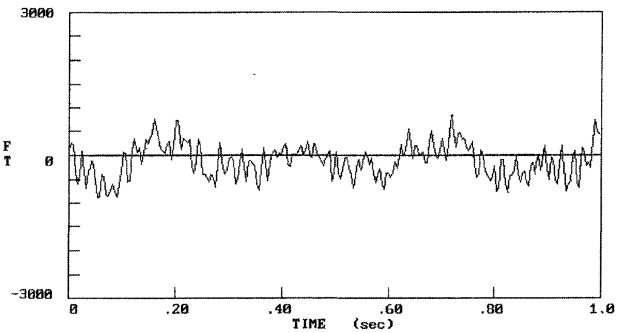

Figure 5. — Neonatal brain MEG measurements following pre-eclamptic pregnancy.

is operated inside a shielded room with low magnetic noise (30-50Ft/√Hz). Mechanical vibrations, which could induce intolerable interfering signals, are avoided by mounting the shielded room and the support of the measurement system on a specially designed concrete foundation. The field sensor is located in cryostat filled with liquid helium (4° K), which can be tilted in two directions so as to be adjusted vertically and have access to any part of the body.

The newborns were usually examined during natural sleep although chloral hydrate (50 mg/kg) was given for sedation in three "normal" neonates to avoid artifacts from eye flickering.

MEG recordings were obtained from the temporal region bilaterally, from four specified points on each side of the scalp, with the babies lying prostrate. (Figure 1). The selection of the measurement points was based on the 10-20 International Electrode Placement System [24], with the T3-T4 standard EEG recording positions being the centers of two respective circles, and all four measurement points on each side being placed diametrically opposite on two vertical diameters going through T3-T4, 1 cm from the center. The SQUID sensor was placed 3 mm above each particular point. Thirty-two consecutive MEG measurements of 1 sec duration each were taken and digitized, with a sampling frequency of 250 Hz, and a bandwidth between 1 and 128 Hz. The MEG records were digitized with an analog-to-digital converter and stored in an IBM-PC computer for off-line Fourier statistical analysis. In all cases the frequency bands were 2-7 Hz.

In order to establish the actual differences between the environmental noise level and the power contained in the MEG spectrum, we averaged all the MEG spectra recorded during each session and compared them with the noise level determined during the same session. Statistical analysis of our results was assessed by the Student's *t-test*.

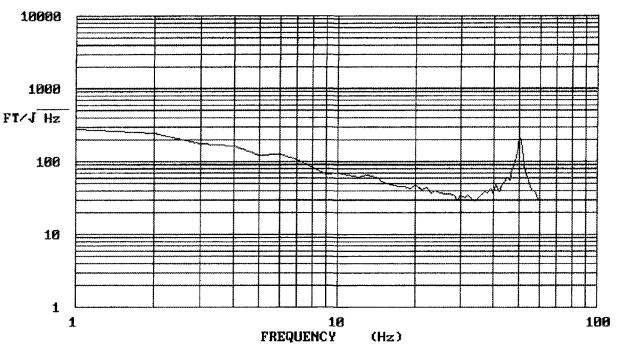

Figure 6. — The spectral amplitudes of the waveforms shown in Figure 5 after statistical Fourier analysis.

Table 1. — *Gravide with pregnancies compliated with pre-eclampsia*

Gestational age (weeks)	Pre-eclampsia	Blood pressure	Proteinuria	Oedema	MEG (ft/√Hz)	Neonatal Weight (Weight percentile)
37	severe	200/110	2+	–	234	w<10th
	severe	190/95	3+	+	243	10th<w<25th
	mild	165/90	Trace	+	155	75th<w<90th
	severe	210/115	3+	+	233	10th<w<25th
	mild	155/105	1+	–	165	75thw<90th
38	mild	150/95	Trace	+	170	75th<w<90th
	severe	195/105	2+	+	244	50th<w<75th
	mild	155/100	1+	–	228	50th<w<75th
	mild	160/90	1+	+	224	50th<w<75th
	severe	195/110	2+	+	243	25th<w<50th
	mild	150/90	Trace	+	175	75th<w<90th
39	mild	150/90	Trace	+	155	75th<w<90th
	severe	185/115	3+	+	248	25th<w<50th
	severe	210/115	2+	+	245	50th<w<75th

Results

In the present study we aimed to present our data from MEG recordings gained from the brains of 44 neonates delivered normally, without any clinical sign of brain damage, which are clearly shown in Figure 2. MEG recordings ranged from 132.5 Ft\√Hz to 248 Ft\√Hz. Specifically, MEG recordings from neonates corresponding to normal pregnancies (n=30) were of lower magnetic power spectral amplitudes (mean 163.2, SD 22.57) (Figures 3 and 4) compared with those gained from neonates corresponding to pregnancies complicated with pre-eclampsia (mean 211.6, SD 37.74) (Figures 5 and 6). The difference between the two groups was statistically significant (Student's t-test, $p < 0.005$).

Table 1 shows the correlation between clinical diagnostic criteria of pre-eclampsia and birth-weight percentiles for all 14 neonates of pre-eclemptic pregnancies. A strong correlation between the degrees of pre-eclampsia, birth-weight and MEG values can be seen.

All 30 neonates in the first subgroup (normal pregnancies) had birth weights over the 75th percentile, umbilical cord pH >7.25 and Apgar scores >7. There were three neonates in this group with comparatively high MEG recordings (178.5, 210, and 225 Ft\√Hz respectively) who were delivered by vacuum extraction.

In the second subgroup (pre-eclamptic pregnancies) there were five neonates with low MEG recordings (from 155 to 175 Ft\√Hz) who all corresponded to mild pre-eclampsia. All five neonates had birth weights between the 75th and 90th percentile, cord-pH between 7.18-7.19 and 1 min Apgar score between 5-7. The remaining nine neonates with the high amplitudes had cord pH between 7.14-7.19 and 1 min Apgar scores between 5-7. There was no significant difference in this subgroup regarding the initial Apgar scores, probably because Apgar score is a subjective variable, estimated by different individuals.

Discussion

It has long been accepted that the measurement and evaluation of magnetic fields that are generated simultaneously with electrical potentials form a promising approach in studying organ function. These are influenced by tissue conductivity much less than electrical potentials are, rendering, therefore, the localization of intracorporeal current sources possible, by means of noninvasive measurements. Single or few channel systems that were used for the investigation in biomagnetism during the past decade are now superseded by multichannel systems with the capability of obtaining true coherent measurements in a reasonable time, so that biomagnetism is now ready for systematic clinical evaluation [25]. Biomagnetic activity has widely been utilized in the study of brain function in adults and became of great help in the management of epilepsy [16-18, 25-27]. Less information exists about biomagnetic activity of the fetal brain [19-22] while for the neonatal brain only very few reports have been published [19, 20].

With the present study we want to trigger scientific interest about the application of biomagnetism in evaluating neonatal brain function. The method of our study and the reliability of our results were based on previous studies where it was suggested that biomagnetism forms a reliable method for describing the brain activity of fetuses, neonates, children and adults [19, 20, 28-31] when compared to other conventional methods of assessment, like EEG, CT and MRI [18, 26]. Our study results present the range of the magnetic power spectral amplitudes gained from term newborns without any clinical sign of brain damage. Moreover, of great interest is the significant difference among the mean values of biomagnetic recordings originating from normal and pre-eclamptic pregnancies (normal pregnancies corresponded to lower spectral amplitudes while pre-eclamptic pregnancies corresponded to higher spectral amplitudes). Pre-eclampsia is an entity directly influencing uteroplacental and fetoplacental circulation resulting, probably in fetal hypoxia and brain dysfunction [3]. Vacuum extraction, dystocy or small gestational age (resulting in delayed brain development) [11] could possibly explain some of the cases with high spectral amplitudes in the "normal" subgroup, while mild types of pre-eclampsia and comparatively higher pH values (7.18-7.19), minimally differentiated from normal conditions, might result in the low spectral amplitudes of the "pre-eclamptic" group. The high spectral amplitudes in the pre-eclamptic group could be related to the comparatively lower pH values (7.14-7.19), which, in turn, might affect brain function, temporarily or permanently. Further investigation of the correlation between variation in gestational age and brain MEG recordings in term newborns, is needed.

It should be pointed out that the MEG recordings gained from "normal" neonates (mean value 163.2) are lower from the ones observed in "normal" fetuses (mean value 376.67) [22]. Similarly, MEG recordings obtained from "pre-eclamptic" neonates (mean value 211.6) are lower from the ones observed in "pre-eclamptic" fetuses (mean value 554,91) [22]. On the contrary, Blum et al. [19] and Wakai *et al.* [20] describe similar magnetoencephalographic recordings from auditory evoked responses for both fetuses and neonates of uncomplicated termpregnancies.

The influence, if any, of sedation on biomagnetic recordings should be further evaluated.

Several techniques are now available for use at the bedside in the first few hours of life, to assess the extent of HIE due to perinatal asphyxia and, accordingly, provide prognostic information. Conventional methods such as EEG, US, CT and MRI present certain disadvantages in everyday practice.

EEG provides a reliable prognostic indicator of the neonate's neurodevelopemental outcome [10] but it is time-consuming, presents difficulty in performance (sometimes it can not be performed on neonates obtunded or receiving sedative anticonvulsant drugs), an experienced neonatologist is needed for the accurate interpretation of the data gained and, generally, electric fields are more distorted by the brain, scull and scalp than magnetic fields are [10, 12, 15, 26].

Diagnostic accuracy, interobserver variability and prognostic value of US, CT, and MRI depend on the kind, localization and extension of brain damage, and differ in preterm and term newborns. US is a practical and low cost method, but has low sensitivity in detecting brain impairment. CT and MRI are of better diagnostic and prognostic values, but they are time and money consuming, need experienced personnel for performance and interpretation and are not suitable for screening or follow-up techniques (5,6,9-12). Modern methods for the assessment of HIE after perinatal asphyxia like CFM and VEP, though of promising value (CFM is given a sensitivity of 0.93 and negative predictive value of 0.90), are still under investigation and their contribution to the prediction of outcome has not yet been established [2, 15].

Biomagnetism is not yet a widely applicable method due to certain drawbacks such as the large size and cost of the device and the need for sedation and an electrically shielded room. Further improvement of the equipment (SQUID) and software used for biomagnetic recordings, so as to become feasible at the bedside, would provide clinical practice with a useful alternative or adjunct tool, suitable for assessing neonatal brain function.

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