OTO-ACOUSTIC EMISSIONS
IN
HEALTHY NEWBORNS
AND
VERY-LOW-BIRTH-WEIGHT INFANTS

RENÉE KOK

Cover: Ear of Dionysios, Syracuse, Sicily.

OTO-ACOUSTIC EMISSIONS IN HEALTHY NEWBORNS AND VERY-LOW-BIRTH-WEIGHT INFANTS

OTO-ACOUSTISCHE EMISSIES BIJ GEZONDE PASGEBORENEN EN KINDEREN MET EEN ZEER LAAG GEBOORTEGEWICHT

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Aan mijn moeder,
aan mijn vader

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CHAPTER 1

GENERAL INTRODUCTION

THE PHENOMENON OF OTO-ACOUSTIC EMISSIONS

Kemp was the first to report about a click-Evoked OtoAcoustic Emission (c-EOAE) in 1978. It is a sound that can be recorded in the sealed outer ear canal after click stimulation of the ear.

For registration of the c-EOAE a probe is used that seals the meatus acoustically (figure 1). The probe contains a telephone presenting the click stimulus. This stimulus is electrically generated by a pulse generator. Also contained in the probe is a miniature microphone for recording the response. The EOAE averager shown in figure 1 is needed to extract the weak c-EOAE from the environmental noise and other bodily generated sounds present in the ear canal. In order to improve the signal to noise ratio, the response signals following repeated stimulation are averaged in synchrony with the stimulus. In a cooperative adult, the recording takes 1 to 2 minutes per ear.

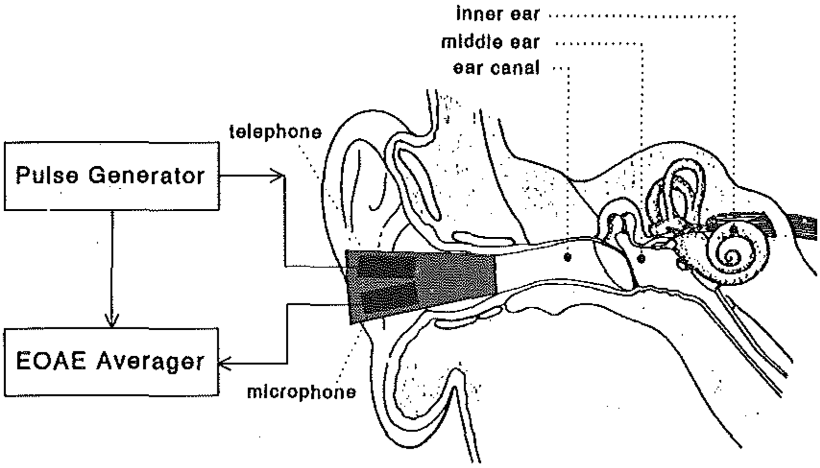


Figure 1
Schematic representation of the equipment needed for c-EOAE recording.

Interestingly, several characteristics of the c-EOAE prove that it is the result of a process of cochlear origin. Figure 2 *(Johnsen and Elberling, 1982a)* shows the difference in response between the artificial ear (Zwislocki coupler, upper trace) and the human ear after click stimulation (second and third trace). The figure represents the sound pressure (vertically) measured as a function of time (horizontally) after click onset. Following decay of the stimulus no more sound can be recorded in the artificial ear. In the human ear however a delayed small ripple is present at 8-10 ms. The bottom trace is a vertical expansion of the second trace and shows the waveform of that ripple more clearly. This waveform is the c-EOAE.

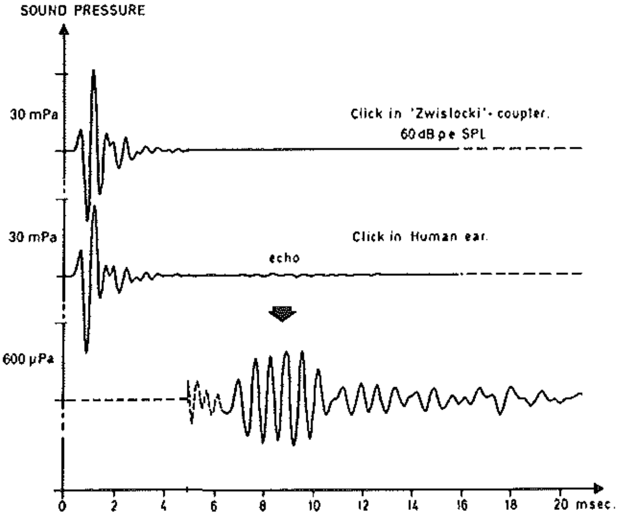


Figure 2
Registration of the sound pressure amplitude (vertically) against time (horizontally) after onset of a click stimulus. The upper trace is recorded in an artificial ear (Zwislocki). The other two in a human ear. The bottom trace is a replica of the middle one, but the sound pressure scale is 50 times magnified and the first 4.5 ms of the trace is blanked. (reprinted from Johnsen and Elberling, 1982a; with permission)

The human middle ear response to a click is normally well damped, and therefore less likely to be the origin of the c-EOAE. The sound pressure in the ear canal will soon decay after the click stimulus is ended, because of the damping quality of the middle ear, as can be seen by the rapid decay of a click stimulus in figure 2. Therefore, a cochlear origin can be suspected for the c-EOAE that is delayed for several milliseconds after the decay of the stimulus. This delay has been important in the discovery of the c-EOAE, which is a low level sound compared to the stimulus, and therefore not easy to detect.

The shape of the c-EOAE waveform is unique to an individual ear. This 'signature' from the ear is maintained in detail for years provided that the middle ear and cochlea remain unchanged *(Kemp, 1978; Grandori, 1983; Johnsen and Elberling, 1982b).*

Soon after the discovery of the c-EOAE, more types of OAEs were uncovered. Spontaneous OAEs (SOAEs) are pure-tone like signals that can be registered in the sealed ear canal without stimulation of the ear at all *(Kemp, 1979; Wilson, 1980; Zurek, 1981).* The SOAE frequencies were reported to be very stable over time, while their amplitudes could change *(Fritze, 1983; Ruggero et al, 1983; Schloth, 1983; Dallmayr, 1985; Cianfrone 1986).*
SOAEs can be synchronised by a stimulus *(vanDijk and Wit, 1987; Kemp 1981; Zurek, 1981; Ruggero et al, 1983; Zwicker and Schloth, 1984).* Hence, a c-EOAE recording can be influenced by SOAEs *(Kemp, 1979; Wit et al., 1981; Zwicker en Schloth, 1984; Probst et al, 1986).*

Next in the historical order of discovery two other types of evoked OAEs were reported. Firstly, the distortion product OAEs (DP-OAEs). These OAEs can be generated when the ear is simultaneously stimulated with two tones, the so called primaries f_1 and f_2. For certain ranges of the frequency ratio and the levels of these two tones, the ear generates extra tones, due to non-linear processing of the primaries. The most prominent DP-OAE has a frequency equal to $2f_1 - f_2$. A DP-OAE can be separated from the much stronger primaries, because the frequency of the DP differs from that of the primaries *(Lonsbury-Martin et al, 1990a).*
Finally, researchers reported about stimulus frequency OAEs (SF-OAEs). This type of emission can be recorded when the ear is stimulated with a single continuous tone. The SF-OAE consists of extra acoustic energy added to the stimulus tone by the ear. Separation between the SF-OAE and the stimulus is possible by virtue of the phase difference that exists between stimulus and SF-OAE. However, this separation is technically very difficult.
Since this study comprises no DP-EOAE and SF-EOAE recordings no further specific description will be presented here.

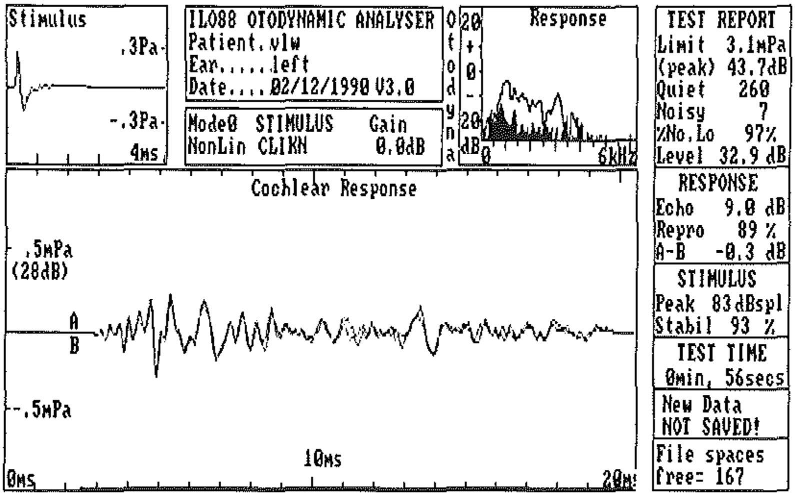
All OAEs are suspected to originate from the cochlea, because the phenomenon is physiologically highly vulnerable. Influences that are known to be damaging to the cochlea, like hypoxia, noise and ototoxic medication abolish OAEs *(Anderson and Kemp, 1979; Kemp, 1982).* In addition, early reports on OAEs stated that the phenomenon was absent in ears with cochlear impairment *(Kemp, 1978).*

In summary, weak sounds of cochlear origin can be recorded in the human outer ear canal shortly after starting the acoustic stimulation of the ear, during stimulation, and some time thereafter. In some ears pure-tone-like sounds are even present spontaneously, that is without any external stimulation.

COCHLEAR PHYSIOLOGY AND OAEs

One of the major sources of interest is the way OAEs could fit in the hearing process. Before the recognition of OAEs it was generally accepted that the sensory physiology of the cochlea reacts passively to sounds. Sounds were assumed to cause a mechanical vibration of cochlear structures. The studies by Von Békésy *(1960)* proved that there exists an orderly mapping of sound frequency to position along the basilar membrane (BM). He noticed that the BM, that is spread out along the coiled cochlea, vibrates maximally at a certain place dependent on the stimulus frequency. This frequency specificity of the cochlea appeared to be the result of a stiffness gradient along the BM. So, like light through a prism, sounds are dispersed in the cochlea. The high frequency sounds cause vibration of the BM at the base of the cochlea, the low frequency sounds more apically. As it takes more time to arrive apically, low frequencies are processed with a slight delay relative to high frequencies.

After stimulation of the ear by a click, which is a sound containing a full spectrum of stimulus frequencies, the c-EOAE waveform shows frequency dispersion too, like the mechanics of the cochlea. The high frequency components of the c-EOAE show up with short delay after the stimulus, i.e. in the first part of the waveform, compared to the low frequency components *(Kemp, 1979)* (figure 3). This finding corroborates the cochlear origin of EOAEs. In fact the c-EOAE waveform is thought to be composed of stimulus frequency re-emissions recorded after cessation of the stimulus. Consequently, the c-EOAE spectrum can be considered the sum of emissions generated on different places along the cochlea. So, in order to get information on the generating capacity of the entire cochlea, we can either record a series of emissions generated by a series of tone-burst stimuli differing in frequency, or we can record the emission generated by a click stimulus (which contains all frequencies at once).



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IL088 OTODYNAMIC ANALYSER
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Date....02/12/1990 V3.0

Mode0  STIMULUS    Gain
NonLin CLIKN       0.0dB

  TEST REPORT
Limit  3.1mPa
(peak) 43.7dB
Quiet    260
Noisy      7
%No.Lo   97%
Level  32.9 dB
   RESPONSE
Echo    9.0 dB
Repro    89 %
A-B    -0.3 dB
   STIMULUS
Peak  83dBspl
Stabil  93 %
   TEST TIME
 0min, 56secs
 New Data
 NOT SAVED!
File spaces
free= 167
```

Figure 3

The result of a c-EOAE recording in a normal hearing adult ear. The upper left panel shows the waveform of the click stimulus on a horizontal time axis. The 'cochlear response' panel shows the c-EOAE waveform on the same time axis, while the first 2.5 ms containing the stimulus are blanked. The sound pressure amplitude scale in this response window is about 1000 times more sensitive than in the stimulus panel.

Rhode *(1978)* reported that the growth in BM vibration increased linearly with stimulus level initially, but non-linearly for the higher stimulus levels. The growth of the EOAE amplitude with increasing stimulus amplitude is in many ears about linear for the lower stimulus amplitudes. For stimuli with moderate to high levels a more and more compressive non-linear growth of the EOAE amplitude with stimulus amplitude exists, eventually leading to a saturated EOAE *(Grandori, 1985; Stevens and Ip, 1988)*. This analogy in behavior of BM vibration and the EOAE amplitude also suggests a cochlear origin of OAEs.

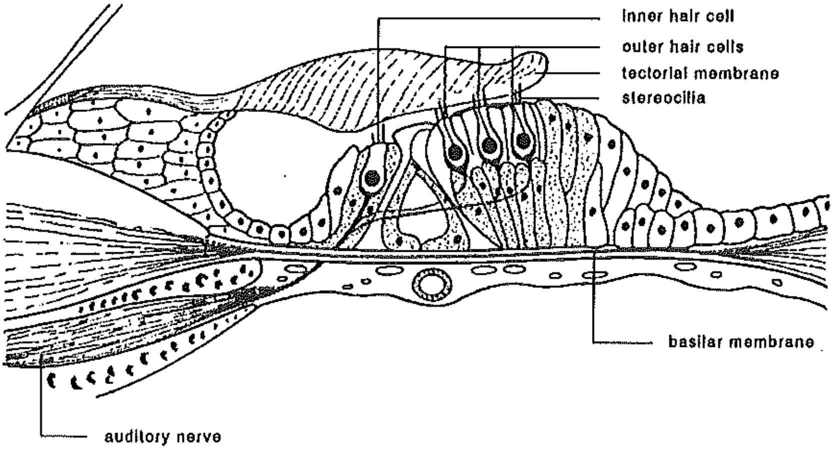


Figure 4
Schematic drawing of a cross-section through the organ of Corti in the cochlea.

In the cochlear models proposed before the era of OAEs, the stereocilia of both IHCs and OHCs were assumed to bend passively in response to the local vibration of the BM (figure 4). This bending of the stereocilia leads to intracellular voltage changes that in turn causes neural spike activity conducted up to the cortex causing the psychophysiological sensation of hearing. However, the human auditory perception shows a frequency selectivity that is much better than could be explained by such a purely passive mechanical system as described above. The non-linear amplitude behavior and the high sensitivity of the cochlea can not be explained by such a system either. However, this was not recognised by then, because at that time no quantification of the mechanical sensitivity could be made by the techniques available. By the end of the 70's it became clear that previous research in cochlear mechanics had been done on damaged cochleas only. The ability to transduce weak sounds had disappeared within minutes after preparation of the cochlea with the previously conventional methods. Yet, many researchers started to think that active processes were needed to explain the high quality of signal processing by the cochlea *(Zwicker, 1979; Kemp and Chum, 1980; Lim, 1986; Neely, 1985)*. Nowadays outer hair cells (OHCs) are thought to play an important role in the probably active process of cochlear frequency selectivity. Unlike inner hair cells (IHCs), the cytoskeleton of OHCs contains important contractile proteins *(Kim, 1986)*. Probably due to this muscle-like facility the length of the OHC varies with its degree of electrical polarization *(Brownell et al, 1985)*. In addition, OHCs appear to be intrinsically tuned to a characteristic frequency, as they are graded in size from the basal (short and wide) to the apical end (tall and slender) of the cochlea *(Brownell, 1990)*. Also the length of the stereocilia on top of the OHCs varies along the BM *(Harrison, 1986)*. The stereocilia of the OHCs are fixated to the tectorial membrane *(Lim, 1986)*, while those of the IHCs are not. Finally, the innervation of the OHCs is predominantly efferent, contrasting to the mainly afferent innervation of IHCs. Figure 5 shows two tuning curves displaying the neural firing threshold level of an IHC for a pure tone stimulus as a function of it's frequency. The two curves are recorded at a basilar position where IHCs are normal for two different conditions: a) in the normal presence of OHCs (dashed line), and b) in total absence of OHCs (solid line). In the damaged condition, without OHCs, the tuning curve has a bowl-shape and lacks a tip *(Liberman and Dodds, 1984)* (figure 5). Disappearance of the tip indicates that the cochlea maps a specific frequency less effectively to a specific place in the damaged region. In addition, the threshold has increased by 40 dB from the tip to the lowest part of the bowl-shaped curve illustrating a dramatic decrease in sensitivity to sound. In summary, it is demonstrated that OHCs significantly enhance the cochlear information before the IHCs actually drive the auditory afferent nerve, and the information is transduced to the cortex.

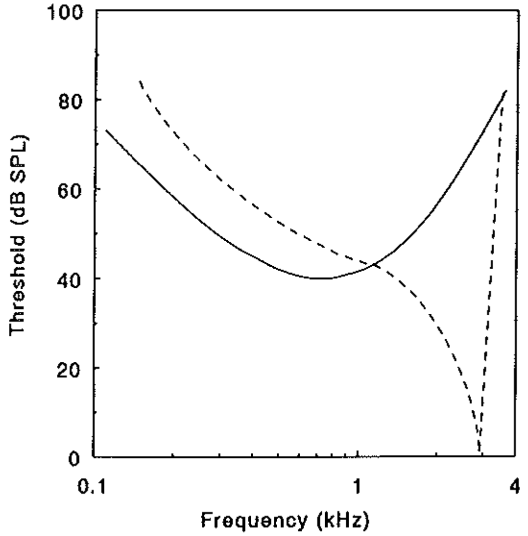


Figure 5
Tuning curve derived from a normal organ of Corti (dashed line), and one after total destruction of OHCs (solid line). The damaged organ of Corti has a bowl-shaped tuning curve picturing loss of sensitivity and of frequency selectivity. (adapted from Liberman and Dodds, 1984)

Additional evidence for a cochlear origin of OAEs is the fact that the phase of an EOAE will inverse as a result of exact phase inversion of the stimulus *(Rutten, 1980; Wit and Ritsma, 1980; Anderson, 1980)*. Using masking techniques sharp OAE tuning curves can be measured *(Wit and Ritsma, 1979; Kemp and Chum, 1980; Zurek, 1981; Zwicker, 1983)*. This means that certain frequency components of the OAE can be suppressed by external tones, representing a frequency specificity as found in the entire auditory system, from auditory nerve fibres up to the cortex.

Since EOAEs do not adapt at higher stimulus rates as strongly as neural phenomena normally do the EOAE generators are generally considered to be at a presynaptic location in the cochlea *(Rutten, 1980; Kemp, 1982)*.

Given the large frequency selectivity of human hearing it was Gold *(1948)* who already proposed a mechanical positive feedback system as the only mechanism imaginable providing such a high selectivity. He also predicted that as a result of this mechanism sounds might be detectable in the external ear canal. The active cochlear model suggests that on top of the passive tuning of a sound, i.e. the local vibration of the BM, the motile activity of the OHCs can amplify this vibration on the basilar membrane *(Davis, 1983; Wilson, 1984; Johnstone et al, 1986; Kim, 1986; Brownell, 1990)*. This is thought to enhance both the sensitivity and frequency selectivity of the cochlea *(Kemp, 1985; Geisler, 1986)*.

Regarding the OAEs now, it is still unclear how they are exactly generated, but it has been generally accepted that they are initiated by the active, frequency specific processing capability of the cochlea. More specifically, it has been suggested that OAEs are caused by irregularities of the active feedback mechanism of the OHCs on the BM. As Ruggero et al *(1983)* stated, the organ of Corti feeds back positively on its segment of the BM and negatively on adjacent segments. If a local OHC loss exists, the adjacent BM segments will obtain less negative feedback, resulting in a relatively too strong oscillation, i.e. OAEs.

Another possibility is that OAEs result from a true amplification of the local BM vibration by the OHCs.

Few researchers however still believe in a purely passive cochlear system that can account for the frequency selectivity and sensitivity of the cochlea *(Allen and Fahey, 1992)*. In such a model the OAE may be generated by reflection of an anterograde travelling wave, resulting in standing waves as mode of vibration of the cochlear partition.

CLINICAL ASPECTS OF OAES

Reason to think of OAEs as objective acoustical signals, which are typical for the healthy cochlea, are the reports of studies in human subjects revealing that OAEs indeed are found predominantly in ears with about normal hearing.

Table 1: c-EOAE prevalence in normal hearing adult ears.

Study	Number of ears	c-EOAE prevalence (%)
Kemp, 1978	15	100
Rutten, 1980	13	92
Grandori, 1983	23	96
Probst et al, 1986	28	96
Bonfils et al, 1988e	105	100
Stevens and Ip, 1988	36	97
Dolhen and Chantry, 1988a	85	89
Dolhen et al, 1991	71	97
Lamprecht, 1991	116	96
Vedantam and Musiek, 1991	100	100

Most studies report a c-EOAE prevalence of 90 to 100% in normal hearing subjects (table 1). Ears with a sensorineural hearing loss exceeding 15-40 dB show no EOAE *(Kemp, 1978; Rutten, 1980; Probst et al, 1987; Bonfils et al, 1988a,b; Stevens and Ip, 1988; Dolhen et al, 1988b; Collet et al, 1989; Lutman, 1989)*. In healthy newborns an EOAE prevalence of 96 to 100% is reported *(Johnsen et al, 1983, 1988; Elberling et al, 1985; Stevens et al, 1987; Bonfils et al, 1988a,b, 1990)*. And Brainstem Electric Response Audiometry (BERA) thresholds appear to correlate rather well with presence or absence of EOAEs in newborns *(Bonfils et al, 1988; Stevens et al, 1990)*.

The EOAE recording appears to be merely a qualitative method for discriminating between a (sub)normal and an abnormal hearing. The level of the EOAE is related to the hearing sensitivity, but the intersubject variance is too high to allow for individual loss assessment. The hearing is normal at frequencies where energy is found in the EOAE response spectrum *(Kemp and Ryan, 1991)*. Lack of spectral energy within a certain frequency region does not necessarily imply that hearing is impaired for these frequencies *(Kemp et al, 1990; Harris and Probst, 1991)*.

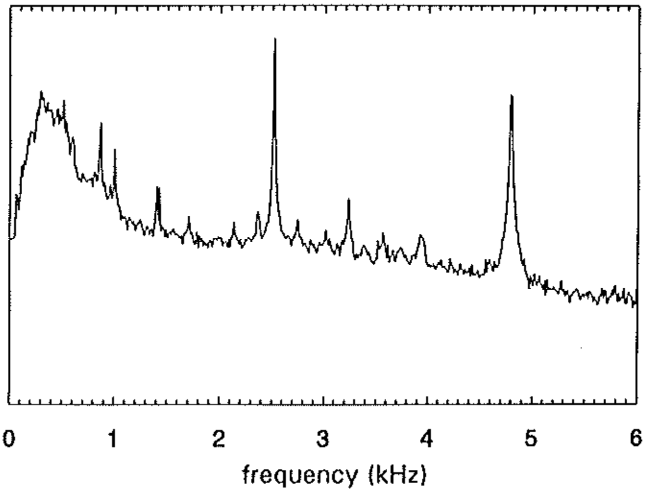


Figure 6
The result of a SOAE recording in the ear of a healthy newborn. The sounds present in the ear canal without any stimulation of the ear are analysed to frequency content. The sound pressure level (vertically, in arbitrary log-units) is determined for frequencies between 0 and 6 kHz (horizontally). The SOAE frequencies are the sharp peaks superimposed on the rather smooth background noise floor.

The implication of the presence of one or more SOAEs (figure 6) is still unclear, but generally they are not present in ears with 25 dB sensorineural hearing loss or more *(Fritze, 1983; Probst et al., 1987)*. In ears of normal hearing adults the prevalence of SOAEs is reported to be about 30% *(Fritze, 1983; Wier, 1984; Kemp et al, 1986; Cianfrone, 1986; Rebillard et al, 1987; Probst et al., 1987)*. Strickland and Burns *(1985)* find 26-31% of ears emitting SOAEs in children between 6 and 12 years. Bonfils et al. *(1989)* report a SOAE prevalence of 68% in infants younger than 18 months of age. Some cases have been reported with cochlear hearing loss and SOAEs in the frequency range of the loss *(Glanville et al., 1971; Huizing and Spoor, 1973; Yamamoto, 1987; Mathis et al., 1991)*. These were all very high frequency SOAEs featuring some more special characteristics. In general, SOAEs can be considered as a reflection of (sub)normal inner ear functioning, detectable in about one third of the normal hearing adult ears.

In addition to a (sub)normal cochlear functioning of the ear, near normal middle ear function is essential for OAE recording. This is understandable since to establish the actual recording of an EOAE, the stimulus has first to be transmitted through the middle ear in the anterograde direction and then the EOAE has to in the retrograde direction. A reduced transmission by the middle ear due to it's malfunctioning abolishes the OAE transmission conceivably. For instance if only the middle ear pressure deviates from normal the EOAE amplitude is already decreased *(Kemp et al, 1986; Dolhen, 1988a)*, particularly the lower frequency components of the EOAE *(Bray, 1989; Kemp et al, 1990; Robinson, 1991; Naeve, 1992; Osterhammel, 1993)*. A study in children with confirmed middle ear dysfunction revealed absent or markedly reduced EOAE amplitudes, while ears with ventilating tubes exhibited EOAE amplitudes lower than from healthy ears, but higher than those of untreated diseased ears *(Owens, 1993)*. Another study in children demonstrated that no EOAE could be recorded in ears with a conductive loss above 20 dB. Where the conductive loss was smaller it appeared impossible to predict whether an EOAE could be recorded or not *(Erwig, 1991)*.
It has also been suggested that the crucial function of the middle ear transmission system, for the detectability of OAEs, accounts for the fact that in adults most SOAEs and the strongest click or tone-burst EOAEs are detected in the 1 to 2 kHz region *(Kemp et al, 1986; Lonsbury-Martin et al, 1990b; Harris and Probst, 1991)*.

Any type of OAE may still be present in patients with a subjective hearing loss over 40 dB, for instance in patients with a pontine angle tumour. Thus, indicating firstly that the OAE reflects a healthy cochlea only, and secondly that in retro-cochlear pathology an OAE may remain recordable probably as long as the cochlear physiology is preserved *(Bonfils and Uziel, 1988d; Lutman, 1989)*.

In general OAEs can be considered as acoustic energy 'leaking' from the healthy cochlea. A healthy middle ear is required for this energy to be detectable. The c-EOAE is reported to be present in almost 100% of ears with a (sub)normal hearing, and seems particularly valuable for screening purposes.

OBJECTIVE AND MOTIVE OF THIS THESIS

The general objective of this thesis is to acquire extended knowledge of the properties of OAEs in neonates. Our motive is the possible application of OAEs for hearing screening in newborns. In the Netherlands the final diagnosis and the start of rehabilitation of infants with moderate to severe hearing loss is on average not completed before the age of 18 months. Yet, we know that in the interest of the development of these infants intervention should best be started as early as possible. In the Dutch situation infants are hearing screened at the age of 9-12 months with the Ewing distraction test. This method detects the (congenital) perceptive hearing losses as well as the much more prevalent conductive losses which are generally acquired in the first year of life. Yet, there is still need for an earlier screening on severe perceptive hearing loss.

Starting our study in 1990 most of the then published studies used no commercial equipment, and relatively small numbers of neonates were examined. We used commercial equipment, the functioning of which is based on two considerations: 1) all sounds that are randomly related to the click stimulus are quenched by a stimulus synchronised averaging mechanism, and 2) amplitudes of sounds responded by the cochlea show a non-linear relation with stimulus amplitude. The ILO88 uses a so called 'non-linear click sequence' to stimulate *(Kemp et al, 1990)*. Eventually only the non-linear phase-locked saturated component of the oto-acoustic response, the c-EOAE is extracted.

The first part of this study *(Chapter 2 to 4)* is conducted in over 1000 healthy newborn ears and aims at describing the feasibility of ear screening with c-EOAEs, the c-EOAE prevalence, and basic c-EOAE features in these neonates.

SOAEs can be phase-locked to a stimulus and therefore are known to influence c-EOAEs. In Chapter 5 a report on the aspects of SOAEs in healthy newborns is given.

In very-low-birth-weight (VLBW) infants two aspects are of interest regarding OAEs. Firstly, VLBW infants are at risk for hearing disability. So, knowing c-EOAE charactersties in this specific group of infants is important for valuing the c-EOAE as a screening tool in these infants. Secondly, it is possible that the inner ear still matures during direct postnatal life in VLBW infants who are often born prematurely. Therefore we studied c-EOAEs in VLBW infants. In Chapter 6 we described factors influencing the feasibility of ear screening with c-EOAEs, the c-EOAE prevalence, and basic c-EOAE features in VLBW infants. In Chapter 7 we studied possible reflections of the developmental changes of the ear on the c-EOAE characteristics.

The general discussion and conclusions are given in Chapter 8.

CHAPTER 2

GROWTH OF EVOKED OTO-ACOUSTIC EMISSIONS DURING THE FIRST DAYS POST PARTUM

A Preliminary Report.

ABSTRACT

Evoked Oto-Acoustic Emissions (EOAEs) were recorded twice in 20 ears of 15 newborns. The recordings were performed in a room of the well baby ward, using the ILO88 in its default setting, i.e. with click stimulation. On the first test occasion, the infants were between 3 and 51 hours of age, and EOAEs were identified in 10 ears. On the second test occasion, while the infants were at least one day older (range 42-107 hrs), EOAEs were present in all ears. The second EOAE was stronger, so the EOAE appeared to grow in the first days post partum. This might be due to middle ear clearance of amniotic fluid, shortly after birth.

The results of the EOAEs of the second examination were compared with 10 EOAEs in adult ears. The response levels of the newborns were significantly higher than in the adults.

The (cross)correlation peak value of the two tests' waveforms is over 0.75, however sometimes only after filtering around the most pronounced emission frequencies.

The study proves that newborns failing the EOAE-screen in the first 24 hours after birth can pass if retested one day later, simply because of growth of EOAE strength.

INTRODUCTION

Kemp *(1978)* discovered the phenomenon of Evoked Oto-Acoustic Emissions (EOAEs) after click stimulation. An EOAE is probably based upon motile activity of the outer hair cells, which amplifies the travelling wave on the basilar membrane. Part of this activity leaks from the cochlea and is transmitted back through the ossicular chain and tympanum. It can be recorded with a miniature microphone in the sealed ear canal.

Most studies report an EOAE prevalence of 90 to 100% in normal hearing *(Kemp, 1978; Wit and Ritsma, 1979; Rutten, 1980; Johnsen and Elberling, 1982b; Grandori, 1983; Probst et al, 1986; Bonfils et al, 1988c; Stevens and Ip, 1988; Dolhen and Chantry, 1988a)*. This value drops with an increasing amount of hearing loss. An ear with a hearing loss exceeding 15-40 dB shows no EOAE *(Kemp, 1978; Rutten, 1980; Probst et al, 1987; Bonfils et al, 1988a,b; Stevens and Ip, 1988; Dolhen and Chantry, 1988b; Collet et al 1989; Lutman, 1989)*. These findings lead some researchers to suggest using EOAEs to screen for inner ear function in newborns *(Johnsen and Elberling, 1983; Elberling et al, 1985; Stevens et al, 1987; Bonfils et al, 1988a-c, 1990; Johnsen et al, 1988)*. They reported an EOAE prevalence in healthy newborns of 96 to 100%. In high risk babies in intensive care, this value amounts 79 to 81% *(Stevens et al, 1987, 1989)*. All of these studies, used custom-made laboratory equipment.

There is at present no appropriate test to screen for hearing impairment in infants. Brainstem Electric Response Audiometry (BERA) is generally accepted as a good method for the early detection of auditory dysfunction, but this test is rather expensive. So it is important to investigate if EOAEs can be applied in mass-screening.

Before EOAE recording can be considered to be a viable screening method, the basic features of EOAEs in healthy newborns have to be studied, as well as the relation between EOAEs and the type and amount of hearing loss.

This paper describes some aspects of the EOAE in 20 newborn ears, compared with those in normal hearing adults. EOAE recording was performed twice in each newborn, to observe the possible changes in the EOAE shortly after birth. The notion that changes would occur was based upon the finding that EOAE prevalence appeared to be age dependent in the first days post partum in a study of about 400 ears of healthy newborns. The recordings were made with commercially available equipment.

MATERIAL AND METHODS

SUBJECTS

EOAEs were recorded twice, with a time interval of at least one day, in 20 ears (9 left; 11 right) of 15 healthy newborns (11 boys; 4 girls). The ages of the newborns varied between 3 and 51 hours (mean 21 h) on the first test occasion, and between 42 and 107 hours (mean 67 h) on the second test occasion, which was at least one day later.

The 10 adult ears (3 left; 7 right) were randomly selected out of a population of 60 ears with clear EOAEs, with a stimulus level recorded in the ear canal of less than 84 dBSPL. This last criterion was taken to get at similar stimulus levels as in the newborn group. The adults (4 men; 6 women) were between 19 and 51 years old (mean 30 yr).

EQUIPMENT

The ILO88 (Otodynamics, London, software Version 3.0) was used in its default settings *(Kemp et al, 1990)*. The newborn probe is sealed into the ear canal using rubber or silicon tubing for the probe tip in the newborns. In the adults a perforated foam ear plug was used as a seal for the adult probe. The stimulus is a click with a duration of 80 μs. The acoustical stimulus waveform is recorded in the ear canal and displayed. The peak-peak sound pressure level is calculated by the ILO88 and displayed too. During the measurement the nonlinear component of the oto-acoustic response waveform is calculated by application of a so called 'non-linear click sequence'. During response acquisition artefact-rejection is applied, the level of which can be manually adjusted. The response is averaged out of 260 accepted sweeps in two subaverages of 130 sweeps over the 2.5-20 ms post-stimulus time interval. The response level is calculated from the grand average and the background-noise level from the difference between the two subaverages. The waveforms of the two subaverages are displayed, as well as the levels of the response and the background noise. As a measure of the reproducibility, the correlation coefficient between the two subaverage waveforms is displayed too. The spectra of the response and the background noise are also displayed and the spectrum of the stimulus waveform can be displayed on command.

PROCEDURES

EOAE recordings in the newborns were made in a separate room, at the well baby ward, that was not sound treated. The examinations were made in the presence of the tester and in most cases the mother. The adults were tested in a quiet, but not "silent" room at the audiological department. The artefact rejection level was adapted to the recording conditions for each ear. This level varied between 43 and 52 dBpeSPL in the newborn group and between 43 and 50 dBpeSPL in the adult group.
Each newborn was examined twice in the first days post partum. The intertest period was at least one day.

Table 1: EOAE recordings, results in newborns and adults.

Subject	Stimulus level dBSPL		Response level dBSPL		Response repro. %		A-B dBSPL		WRL dBSPL		EOAE		Intertest correlation
	1	2	1	2	1	2	1	2	1	2	1	2	
1-R	84	79	12	28	29	98	13	8	4	27	-	+	0.18
2-R	77	75	10	16	37	84	10	9	4	14	-	+	0.10
3-R	83	83	22	35	92	95	11	21	20	33	+	+	0.41
4-R	83	82	9	14	50	81	7	7	5	11	-	+	0.59
L	84	82	8	13	33	57	8	10	3	8	-	+	0.35
5-R	81	79	33	31	99	99	8	9	32	31	+	+	0.85
L	83	80	15	30	63	98	11	11	9	30	+	+	0.08
6-R	81	83	8	23	-22	95	13	10	2	22	-	+	0.13
L	79	79	7	21	-12	95	11	8	1	20	-	+	0.02
7-R	83	83	16	24	83	98	8	7	13	23	+	+	0.70
L	86	83	4	17	-29	83	10	9	1	14	-	+	0.00
8-R	79	76	11	18	51	80	10	12	6	15	+	+	0.06
9-R	80	79	8	17	39	87	7	8	3	15	-	+	0.28
10-L	80	80	15	16	84	84	7	9	12	14	+	+	0.04
11-L	80	78	20	21	93	96	8	7	18	20	+	+	0.59
12-R	85	79	6	18	-3	92	9	7	0	16	-	+	0.14
L	80	80	8	18	37	90	7	7	3	16	-	+	0.15
13-R	77	78	13	13	67	84	9	5	9	11	+	+	0.71
14-L	80	79	29	32	92	99	18	9	27	32	+	+	0.66
15-L	96	78	23	29	93	99	11	8	21	29	+	+	0.58
Newborn mean	82	80	14	22	49	90	10	9	9	20			
Adult mean		82		11		87		2		10			

1 = first test; 2 = second test; R = right ear; L = left ear.

DATA PROCESSING

Qualitatively the presence or absence of an EOAE in the response waveform was scored visually. The response spectrum was subjectively scored as to the relative strengths of the frequencies above and below 3 kHz.

The following standard available quantitative measures of the stimulus and the response were used: the levels of the stimulus (displayed on the ILO88 as 'Peak'), the response level ('Echo'), and the background noise level ('A-B'), and the reproducibility of the response ('Repro'). To quantify the strength of the response, the Weighted Response Level (WRL) was used, defined as the product of the absolute value of the reproducibility (%) and the response level. In this way a measure of the combined level and quality of the recording is defined *(Van Zanten et al, 1990)*.

For the calculation of the intersession waveform reproducibility a pascal program was written, that used the ILO88 data files as input. The program calculated the cross-correlation function of the waveforms acquired in the two sessions. This was necessary to allow for small time-shifts of the waveform between sessions. If no such time-shift was present, the reproducibility figure equalled the reproducibility calculated by the intertest comparison procedure that is built in to the ILO88.

RESULTS

The results of EOAE measurements in newborns and adults are shown in table 1.

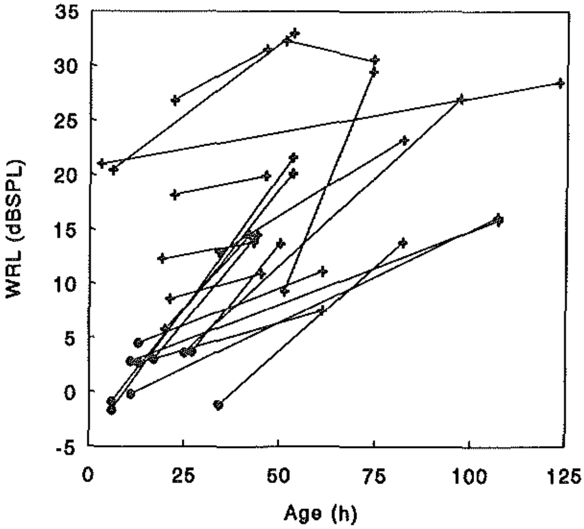


Figure 1
Weighted Response Levels and age in hours for the EOAEs of both test occasions in 20 newborn ears, connected with straight line segments. Visual scores of EOAE absence or presence are indicated by '●' and '+' respectively.

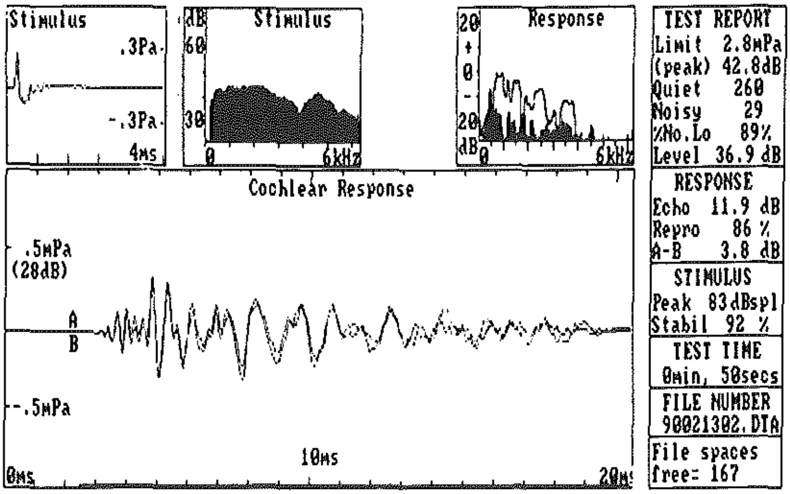
NEWBORNS

An EOAE was present in 10 out of the 20 ears on the first test occasion and in all cases on the second test occasion. The age range at the first test was 3 to 51 hours and for the second 42 to 107 hours. As a more objective measure of the EOAE strength, the WRL was determined. In all except one ear the WRL was higher on the second test occasion; this one ear had a high WRL the first test occasion already. Figure 1 shows the WRL found on both test occasions connected with straight line segments.

Restricting ourselves now to the 20 EOAEs of the second examination, we measured a mean stimulus level in the ear canal during the EOAE recording of 80 dBSPL. The mean response level amounted to 22 dB (standard error 2 dB), while the mean background noise level was 9 dBSPL. The mean WRL was 20 dBSPL (standard error 2 dB). The mean time necessary to record an EOAE was 3 minutes and 30 seconds (range: 88-421 s).

ADULTS

The EOAEs recorded in 10 adult ears had a mean stimulus level measured in the ear canal of 82 dBSPL. The mean response level was 11 dB (standard error 1 dB), while the background noise was only 2 dB. The mean WRL was 10 dBSPL (standard error 1 dB), the mean time taken for each test 58 seconds (48-82 s). An example of an EOAE recorded in an adult ear is shown in figure 2.



TEST REPORT
Limit 2.8mPa
(peak) 42.8dB
Quiet 260
Noisy 29
%No.Lo 89%
Level 36.9 dB

RESPONSE
Echo 11.9 dB
Repro 86 %
A-B 3.8 dB

STIMULUS
Peak 83dBspl
Stabil 92 %

TEST TIME
0min, 50secs

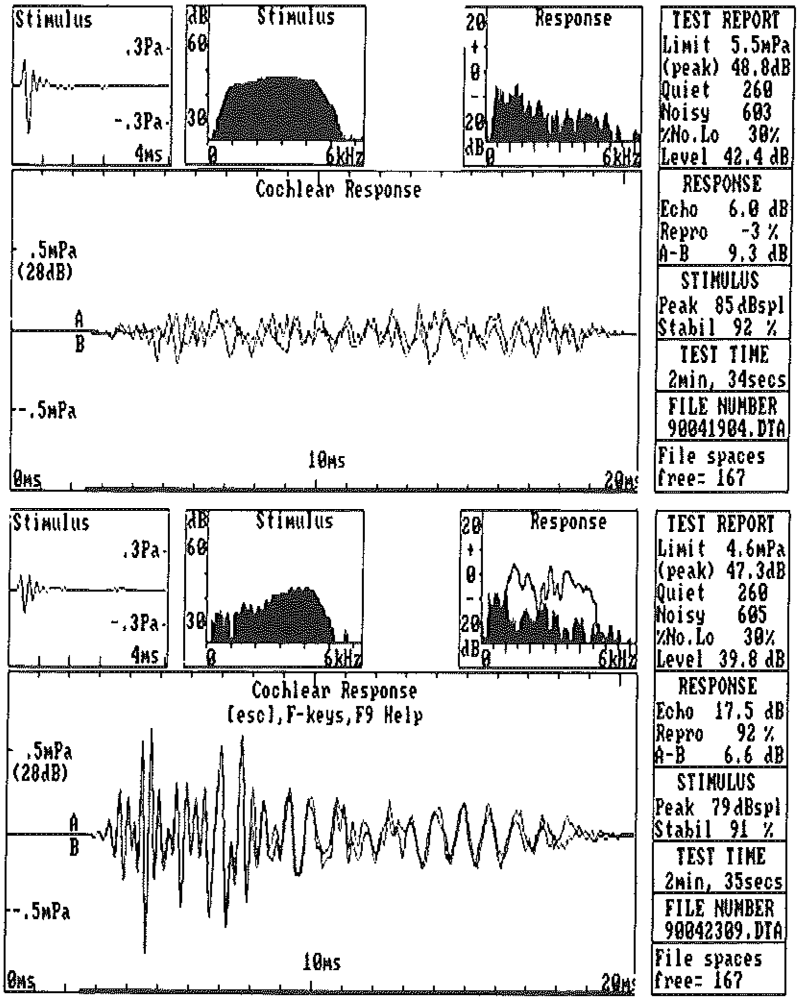
FILE NUMBER
90021302.DTA

File spaces
free= 167

Figure 2
EOAE recorded in an adult ear.

WAVEFORM STABILITY IN NEWBORNS

The correlation between the two response waveforms, resulting from the test and retest, respectively, in the newborns ranged from 0.00 to 0.59 for ears with no recordable EOAE



TEST REPORT
Limit 5.5mPa
(peak) 48.0dB
Quiet 260
Noisy 603
%No.Lo 30%
Level 42.4 dB

RESPONSE
Echo 6.0 dB
Repro -3 %
A-B 9.3 dB

STIMULUS
Peak 85dBspl
Stabil 92 %

TEST TIME
2min, 34secs

FILE NUMBER
90041904.DTA

File spaces
free= 167

TEST REPORT
Limit 4.6mPa
(peak) 47.3dB
Quiet 260
Noisy 605
%No.Lo 30%
Level 39.8 dB

RESPONSE
Echo 17.5 dB
Repro 92 %
A-B 6.6 dB

STIMULUS
Peak 79dBspl
Stabil 91 %

TEST TIME
2min, 35secs

FILE NUMBER
90042309.DTA

File spaces
free= 167

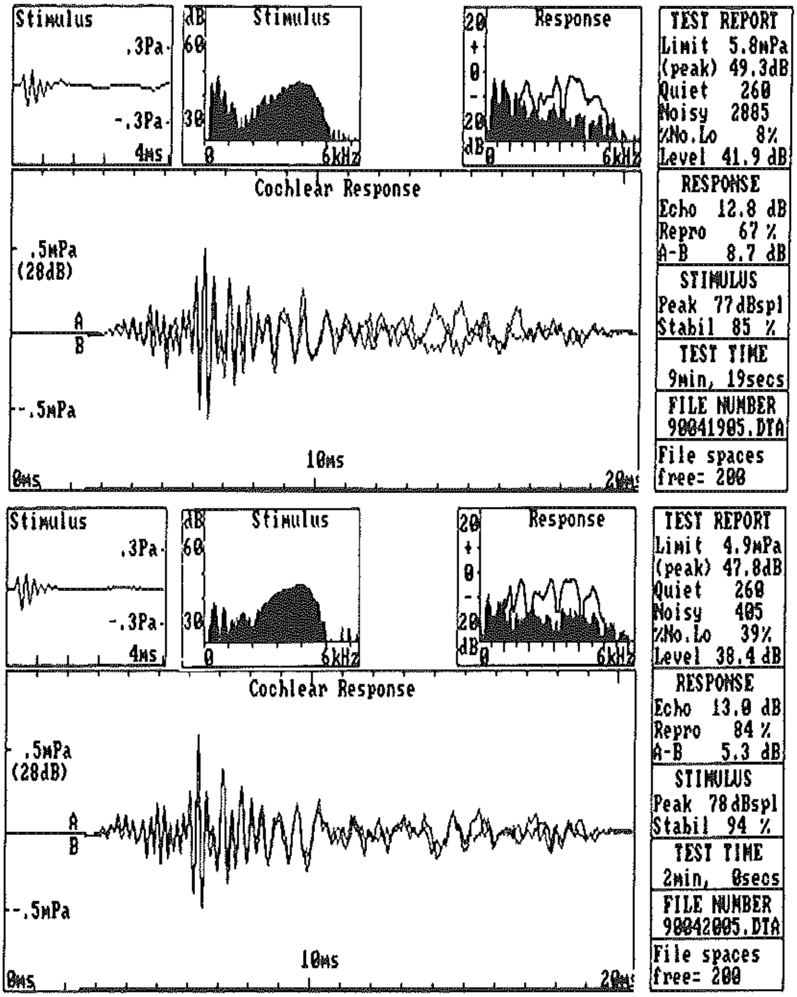
Figure 3

Result of test and retest EOAE recording in a newborn ear. The upper response shows no EOAE, but the lower response shows a clear EOAE (subject 12-R in table 1).

in the first instance, but with a clear EOAE in the retest. An example of such an EOAE pair is shown in figure 3. The correlation coefficient varied between 0.04 and 0.85 for ears with twice a clear EOAE (fig.4).

DISCUSSION

The prevalence of EOAEs in 20 ears of healthy newborns, ranging from 3 to 51 hours of age was only 50%, while this value rose to 100% in the same ears, when these newborns were



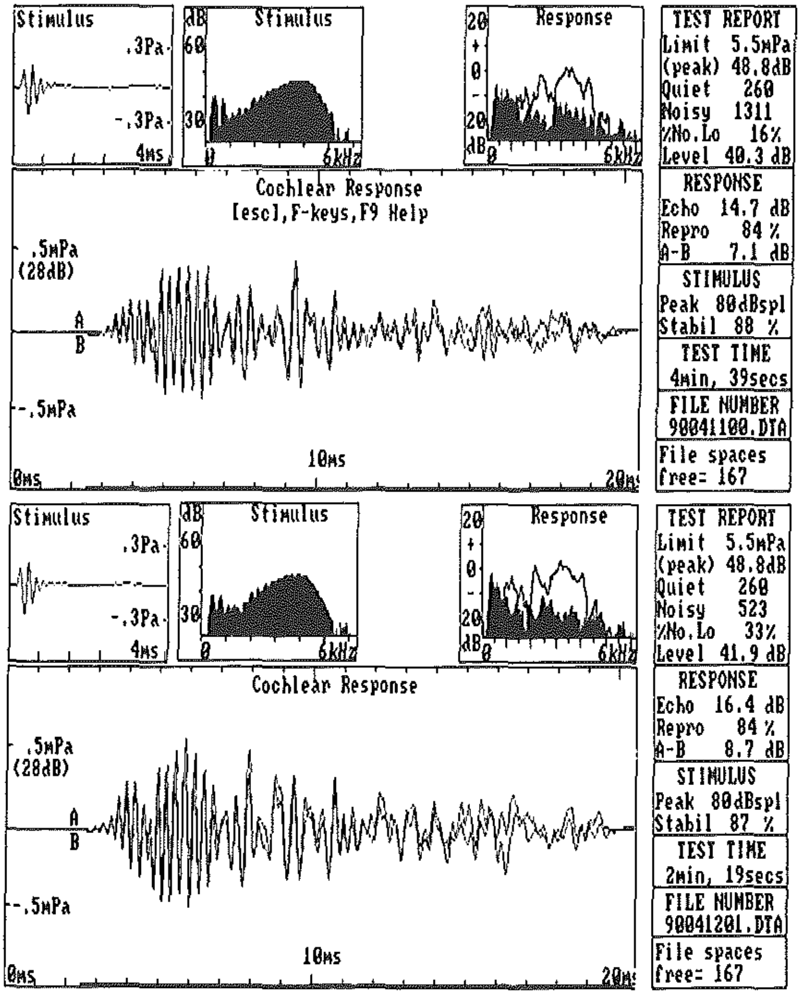
TEST REPORT
Limit 5.8mPa
(peak) 49.3dB
Quiet 260
Noisy 2885
%No.Lo 8%
Level 41.9 dB
RESPONSE
Echo 12.8 dB
Repro 67 %
A-B 8.7 dB
STIMULUS
Peak 77dBspl
Stabil 85 %
TEST TIME
9min, 19secs
FILE NUMBER
90041905.DTA
File spaces
free= 200

TEST REPORT
Limit 4.9mPa
(peak) 47.8dB
Quiet 260
Noisy 405
%No.Lo 39%
Level 38.4 dB
RESPONSE
Echo 13.0 dB
Repro 84 %
A-B 5.3 dB
STIMULUS
Peak 78dBspl
Stabil 94 %
TEST TIME
2min, 0secs
FILE NUMBER
90042005.DTA
File spaces
free= 200

Figure 4

EOAEs of test and retest in a newborn ear. The ILO88 correlation coefficient is 0.71 (subject 13-R in table 1).

at least 24 hours older. The response got stronger in the first days post partum so the WRL got higher. The speed of growth of the response level - i.e. the slope of the line segments in figure 1 - varies strongly between ears, even in one subject (fig.1, table 1). The growth of the response level might be due to changes in the middle ear function shortly after birth, when the middle ear must be cleared of (amniotic)fluid. Regarding the screening purpose of EOAE recordings, this would imply that the newborns should not be examined too soon after birth.



TEST REPORT
Limit 5.5mPa
(peak) 48.8dB
Quiet 260
Noisy 1311
%No.Lo 16%
Level 40.3 dB

RESPONSE
Echo 14.7 dB
Repro 84 %
A-B 7.1 dB

STIMULUS
Peak 80dBspl
Stabil 88 %

TEST TIME
4min, 39secs

FILE NUMBER
90041100.DTA

File spaces
free= 167

TEST REPORT
Limit 5.5mPa
(peak) 48.8dB
Quiet 260
Noisy 523
%No.Lo 33%
Level 41.9 dB

RESPONSE
Echo 16.4 dB
Repro 84 %
A-B 8.7 dB

STIMULUS
Peak 80dBspl
Stabil 87 %

TEST TIME
2min, 19secs

FILE NUMBER
90041201.DTA

File spaces
free= 167

Figure 5

EOAEs of test and retest in a newborn ear. The ILO88 correlation coefficient is 0.04, the cross-correlation peak value is 0.77 (subject 10-L in table 1).

Marked differences appear when the 20 EOAEs of the second examination of the healthy newborns are compared with 10 EOAEs in adults. The mean stimulus levels of 80 and 82 dBSPL, for newborns and adults respectively, are comparable, but the response levels in the newborns are significantly higher (22 versus 11 dBSPL). Bray and Kemp *(1987)* suggested that a reason for this may be the smaller ear canal volume in newborns.

We envisage another factor for the EOAE level difference between newborns and adults and that is the greater prevalence of Spontaneous Oto-Acoustic Emissions (SOAEs) in newborns. In normal adult ears the SOAE prevalence is reported to be 25 to 30% *(Fritze, 1983; Wier,* *1984; Kemp et al, 1986; Cianfrone, 1986; Probst et al, 1987)*, while in infants younger than 18 months of age this value is 68% *(Bonfils et al, 1989)*. When recording an EOAE the click stimulus synchronizes SOAEs if present *(Kemp, 1981; Ruggero, 1983; Norton and Neely, 1987)*. Bonfils et al. *(1990)* reported two types of EOAE spectrum in newborns, a wide continuous frequency band alone or with isolated narrowband frequency peaks. The detection threshold of the EOAEs was significantly lower for the EOAEs with isolated peaks in their spectrum, because the overall response level was higher. The isolated peaks in the EOAE-spectrum were previously associated with the presence of SOAEs *(Wit et al, 1981)*. Given the higher prevalence of SOAEs in newborns, we expect on average the EOAE-levels in newborns to be higher than in adults. Real evidence may be provided by determination of the correlation between SOAE and EOAE amplitudes.

EOAEs in newborns show on average a stronger high frequency content (>3 kHz) compared with adults, in whom the response is mainly low frequent (<2.5 kHz) (fig. 1, 2 and 3). However, also the stimulus spectra in newborns show on average a stronger high frequency content than in adults, while the low frequent stimulus content in newborns seems less strong compared with adults. The question remains to what extent the differences in stimulus spectra can account for the differences in the response spectra. Studies on input-output functions will have to be done to answer this question.

Correlation coefficients quantifying the similarity of the two response waveforms in newborns ranged only from 0.04 to 0.85 for ears with a clear EOAE on both occasions. This is in disagreement with reports on the stability of the EOAE waveform *(Kemp, 1982; Grandori, 1983)*. However correlation in 6 out of the 10 ears ranged from 0.58 to 0.85. In figure 5 the waveform is similar in both examinations, while the intertest correlation is only 0.04. This leads to the question, whether this low intertest correlation in some cases is due to a real change in waveform morphology, or the exact definition of the "repro"-figure in the ILO88 equipment. When we cross-correlated these two waveforms the cross-correlation peak value amounted to 0.77 at a non-zero delay. The ILO88 "repro"-figure equals the cross-correlation coefficient at zero delay. On the remaining three EOAE pairs with low correlation coefficients, we attained similar cross-correlation results in two pairs, but only after filtering around the most pronounced emission frequencies, which means that at least some frequency bands of these EOAE pairs are highly correlated as well. So after allowing some time-shift and spectral changes, in 9 of the 10 cases the intertest correlation was higher than 0.77.

CONCLUSION

1- The EOAEs in newborns grow stronger in the first days post partum. When using the ILO88 for ear screening in newborns the examination should therefore not been done immediately after birth. Compared with adults the response in newborns appears stronger and contains more high frequency energy.

2- The stability of the waveform as such in the first days of life is not very strong, but allowing for time-shift, highly stable frequency bands are present.

CHAPTER 3

CLICK-EVOKED OTO-ACOUSTIC EMISSIONS IN 1036 EARS OF HEALTHY NEWBORNS

ABSTRACT

Click Evoked Oto-Acoustic Emissions (EOAEs) were recorded in 1036 ears of healthy newborns and in 71 normal hearing adult ears.

Newborns aged between 3 and 238 h were examined in a separate but not silent room of the obstetric ward. The adults were tested in a quiet but not sound treated room. The recordings were more difficult in the newborn than in the adult, which was mirrored in recording parameters such as the duration of measurement (up to 7 min in newborn versus 1-2 min in adult ears). Recording was always successful in adults, while retests were necessary in 4% of newborns. Also the artefact-rejection level and the stimulus stability were more favourable in adults. Still, EOAE recording for screening purposes in newborns seems feasible.

Response levels in newborns (range 1.6-38.6; mean 20.2 dBSPL) appear to be higher than in adults (range 2.7-20.6; mean 12.8 dBSPL).

The overall prevalence of EOAEs in newborns amounted to 93.4%, and appeared to be age related. It rises from 78% in ears from newborns younger than 36 h to 99% in ears of newborns older than 108 h. This rise may be related to the middle ear clearance of amniotic fluid in the first days post partum. The prevalence in newborns older than 3-4 days is comparable with the prevalence of 97.2% in the adults. Therefore, newborns should not be screened before the age of 4 days.

In search of an objective EOAE detection variable, the prevalence of EOAEs for different age groups was calculated for various criterion-values of reproducibility. These prevalences were compared to subjectively-scored EOAE-prevalences in the same age groups. A reproducibility criterion of about 50% appears to be useful for mass-screening in newborns.

INTRODUCTION

In 1978 Kemp reported the Evoked Oto-Acoustic Emission (EOAE), an audiofrequency signal after click stimulation originating in the cochlea, and transmitted through the ossicular chain and tympanum back into the ear canal. The EOAE-phenomenon is probably based upon motile activity of the outer hair cells, which amplifies the travelling wave on the basilar membrane *(Davis, 1983; Wilson, 1984; Johnstone et al, 1986)*. In adult ears the EOAE prevalence is reported to be inversely related to the amount of hearing loss. According to Kemp in 1978 and other researchers, an ear with a hearing loss exceeding 15-40 dB shows no EOAE *(Kemp, 1978; Rutten, 1980; Probst et al, 1987; Bonfils et al, 1988a,b; Stevens and Ip, 1988; Dolhen and Chantry, 1988b; Collet et al 1989; Lutman, 1989)*. Because of these findings, and the objectivity and simplicity of an EOAE measurement, EOAE recording in newborns promises to be a method for ear function screening. Before EOAE recording can be used as a viable screening method, the basic features of EOAEs in healthy newborns have to be studied.

The prevalence of EOAEs in newborns is reported to be close to 100% (table 1), although the number of ears tested in these studies was not very large. All studies used custom laboratory equipment, and the measurements were done in a silent room, except those by Bonfils et al *(1990)*, who measured at the obstetric department.

Using commercially available equipment, the aims of this study were:

1- To study the conditions influencing the feasibility of a large scale application of the EOAE in ear function screening.
2- To describe some basic features of the newborn EOAE and to compare these features with those found in adults using the same equipment.
3- To determine the prevalence of EOAEs in a larger number of healthy newborns.

Table 1: Results of reported studies on the prevalence of EOAEs in newborns.

STUDY	AGE	EARS	EOAE
Johnson et al. (1983)	2 - 4 days	20	100%
Elberling et al. (1985)	2 - 4 days	100	100%
Stevens et al. (1987)	2.87 days	51	96%
Bonfils et al. (1988a)	2 days - 12 months	30	100%
Johnson et al. (1988)	2 - 4 days	200	100%
Bonfils et al. (1990)	0 - 4 days	100	98%

MATERIAL AND METHODS

SUBJECTS

Newborns

EOAEs were recorded in 1036 ears of healthy newborns, admitted to the obstetric ward after birth. Infants scoring positively on the high risk register for hearing disability were excluded *(Joint Committee on Infant Hearing, 1983)*. We assume that all babies included have normal sensorineural hearing sensitivity. The age at testing varied between 3 and 238 hours (mean 67 h). For practical reasons, most of the newborns were tested at the age of about 2 days. 572 of the ears were from boys, and 464 from girls. The gestational age of the infants varied between 34 and 43 weeks (mean 39 weeks), while their birth weights were between 2030 and 5070 gram (mean 3280 g).

Adults

EOAEs were recorded in 71 ears of adults with a normal pure-tone audiogram (no air-conduction threshold exceeding 15 dBHL at 0.25 through 4 kHz, 20 dBHL at 8 kHz; mean air-conduction threshold ≤ 7.5 dBHL). Their ages varied between 7 and 55 years (mean 27 yr). 31 ears were from men, while 40 ears were from women.

EQUIPMENT

In this study the ILO88 (Otodynamics, London, software Version 3.0) in its default setting was used for EOAE assessment *(Kemp et al, 1990)*. The stimulus is a click with an electrical duration of 80 μs. The amplitude of the electrical click waveform fed into the earphone is fixed but 20 dB weaker in the baby probe than in the adult one.

The acoustical stimulus waveform is recorded in the ear canal and displayed in a 'check probe-fit' routine first. A good fit has been achieved when there is minimal noise leakage into the meatus as indicated by a 'noise bar'. When the probe fit is judged to be good enough the stimulus waveform is as click-like and the spectrum as flat as possible. Then response averaging starts on the operator's command.

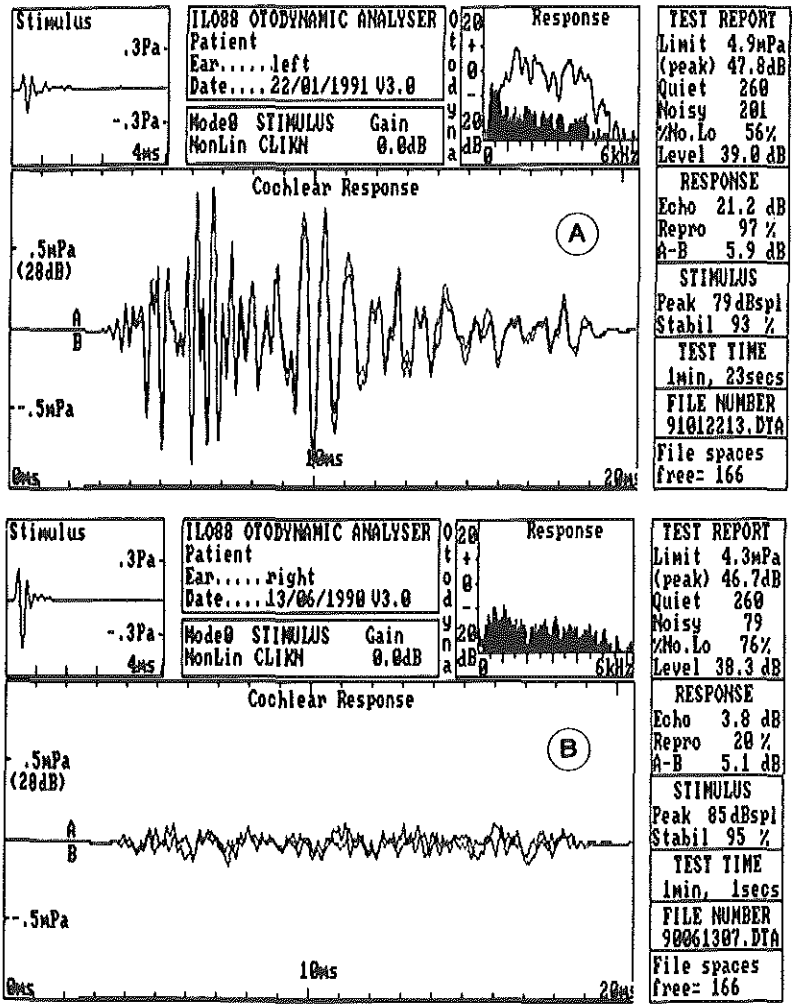
During the check-fit procedure and response averaging, artefact-rejection is applied, the criterion-level of which can be manually adjusted between 33.3 and 54.8 dBSPL. Obviously, the completed averaged response will be less noisy with a lower criterion value of the artefact rejection mechanism, but the measurement duration will be greater. During the check-fit procedure an acceptably low trigger rate of the artefact-rejection is the decision criterion for the operator to start the measurement. The numbers of responses accepted and rejected by artefact rejection are displayed and updated during averaging.

During the measurement the ILO88 uses a so called 'non-linear click sequence' *(Kemp et al, 1990)*. This is done to cancel all components of the recorded signal whose strength is linearly related to the amplitude of the stimulus and whose phase is exactly locked to the phase of the stimulus. The response of the middle ear to the stimulus is assumed to be phase-locked and linear. Phase locking of the inner ear response was reported previously *(Wit and Ritsma, 1980; Anderson, 1980)*. The amplitude of the inner ear response is reported to be strongly nonlinearly related to the stimulus amplitude *(Kemp, 1978; Rutten, 1980; Wit and Ritsma, 1980)*.

Each stimulation sweep of the ILO88 consists of 4 clicks with an inter-click interval of 20 ms. The first 3 clicks have the same sign and amplitude, and the fourth click is of opposite sign and has an amplitude three times as large. After the four responses to the four clicks in the sequence have been summated, only the non-linear phase-locked component of the oto-acoustic response remains.

During the measurement the stability of the stimulus, and therefore of the probe-fit, is indicated on the screen by a 'traffic light'. Its colour is coded every second from the time-domain cross-correlation of the initial and the most recently acquired waveforms of the first click in a stimulation sweep. If the 'light' turns red the probe should be refitted or the measurement restarted.

The final result is averaged out of 260 sweeps alternately accepted in two sub-averages of 130 sweeps. Both these waveforms are windowed over the 2.5-20 ms post-stimulus time-interval and displayed ('A', 'B', figure 1). The rms response level ('Echo') is calculated from the grand average and the rms background noise level ('A-B') from the difference



```
IL088 OTODYNAMIC ANALYSER
Patient
Ear.....left
Date....22/01/1991 V3.0
Mode0 STIMULUS    Gain
NonLin CLIKN     0.0dB

TEST REPORT
Limit  4.9mPa
(peak) 47.8dB
Quiet    260
Noisy    201
%No.Lo   56%
Level 39.0 dB
RESPONSE
Echo  21.2 dB
Repro   97 %
A-B    5.9 dB
STIMULUS
Peak  79dBspl
Stabil  93 %
TEST TIME
1min, 23secs
FILE NUMBER
91012213.DTA
File spaces
free= 166
```

```
IL088 OTODYNAMIC ANALYSER
Patient
Ear.....right
Date....13/06/1990 V3.0
Mode0 STIMULUS    Gain
NonLin CLIKN     0.0dB

TEST REPORT
Limit  4.3mPa
(peak) 46.7dB
Quiet    260
Noisy     79
%No.Lo   76%
Level 38.3 dB
RESPONSE
Echo   3.8 dB
Repro   20 %
A-B    5.1 dB
STIMULUS
Peak  85dBspl
Stabil  95 %
TEST TIME
1min,  1secs
FILE NUMBER
90061307.DTA
File spaces
free= 166
```

Figure 1

Two results of the EOAE recording in healthy newborns. A The response waveform of a visually scored definite 'EOAE'. B The result was scored as 'no EOAE'. See the text for the explanation of most of the annotations given with the responses.

between the two subaverages. As a measure of reproducibility, the cross-correlation coefficient between the two subaverage waveforms is displayed too. The spectra of the response and the background noise are also displayed. The response spectrum shown is the calculated cross-power spectrum of the two subaveraged waveforms. The noise spectrum is the Fourier transform of the difference of the two subaveraged waveforms. The final stability score of the stimulus and the peak sound pressure level of the first click in the final stimulation sweep are calculated. The final numbers of sweeps accepted and rejected are displayed. The spectrum of the stimulus can be displayed optionally on key press.

The sound pressure measurements by the ILO88 are based on a fixed sound pressure to voltage conversion factor calibrated in a 2-cc cavity. Due to inter-transducer sensitivity variation the inaccuracy on the sound pressure measurement is 3 dB at maximum, according to the ILO88 manual. We checked the sensitivities of several microphones (2 adult and 3 baby probes). A tonal stimulus with a duration of 20 ms produced by an audio stimulator (Medelec AS10) was transmitted into an anechoic test chamber (Brüel & Kjaer type 4222). The actual stimulus level was measured by a calibrated instrument (Brüel & Kjaer type 2218). For the frequencies 1, 1.5, 2, 3, 4, and 6 kHz the response level measured by the ILO88 in the nonlinear mode was compared with the actual stimulus level. With all probes at all frequencies the absolute measurement error of the ILO88 was less than 6 dB. For each probe the average (over frequencies) of the ILO88 absolute measurement error was less than 3 dB.

In the calculation of the response amplitude by the ILO88, it is assumed that the amplitude of the emission is totally saturated at the levels of the stimulus used. In that case the sound pressure amplitude of the emission can be calculated from the measured nonlinear component. In case of a non-saturated input-output relation the calculated emission amplitude is incorrect. In the extreme case of linear input-output relation the response to the 'nonlinear click sequence' is zero, i.e. the emission may be present, but is not detected with the ILO88 in the setup used.

In newborns the first version of the newborn probe was used, one without specially designed disposable tips. It was sealed into the ear canal with a piece of a rubber or silicon tube around the probe tip. In adults, the adult probe was used, with a perforated foam ear plug as a seal.

PROCEDURES

The EOAE recordings in newborns were done by the first author. For training purposes EOAEs were acquired in 200 adult ears first. After having gained experience in these 200 normal and hearing impaired ears, we felt sure about the reliability of our scoring presence or absence of an EOAE. Next the same was done in 80 newborn ears. Then the actual data acquisition was started.

EOAE recording experiments in the newborns were done in a separate room in the obstetric ward. The infants were lying in their cribs in various positions. Most of the infants appeared to be asleep, some were awake and calm or slightly restless. The room was not sound treated. In most cases the mother was present during the examinations.

The EOAEs in adult ears were recorded in a quiet, but not sound treated room of the audiological department.

The success rate of the EOAE recording in newborns was scored in 558 consecutively examined ears.

The analyses below are based upon one EOAE recording per ear. If an ear was examined more than once, only the data of the last recording were included.

Of each recording (figure 1) the stimulus level ('Peak'), the stability of the stimulus ('Stabil'), the artefact- rejection level ('Limit(peak)'), and the measurement time were registered ('Test time').

DATA PROCESSING

Subjective EOAE score

The presence or absence of an EOAE was scored visually by the first and second authors as showing an 'EOAE', 'a doubtful EOAE', or 'no EOAE'. The important factors in this manner of scoring were the response waveform (figure 1), its reproducibility (displayed on the ILO88 as 'Repro') and the relative strength of the frequencies in the spectrum of the response, arising above the background noise (see the 'Response' panel of figure 1). Thus an ear with an EOAE shows a reproducible response waveform and obvious peaks in the response spectrum (figure 1A). A response without an EOAE has a low reproducibility and no peaks in the response spectrum above the background noise (figure 1B). We also scored 'EOAE' for those infrequent responses of which the waveform is reproduced only for one or two segments of the 20 ms time-window and the spectrum shows only one or two narrow bands rising above the background noise. The reproducibility of these responses is moderate, because it is calculated from the whole response waveform, but when the moderate to high reproducibility of an EOAE recording was based upon the first milliseconds of the response and the stimulus level during the measurement had been high, we preferred to score it a stimulus artefact, and not an EOAE.

Artifacts which are synchronous with the stimulus are unlikely, because of the nonlinear analysis procedure of the ILO88.

Artifacts non-synchronous with the stimulus are unlikely also, because they yield a low reproducibility of responses.

Objective EOAE variables

For each response, its level ('Echo'), the reproducibility ('Repro'), and the background noise ('A-B') were obtained.

RESULTS

FEASIBILITY

In only 4% of the newborn ears did we fail to perform the test because of restlessness, and a second attempt was always successful. The duration of measurement was up to 7 minutes for 80% of the ears tested. Not always up to 260 sweeps were averaged, but these recordings always showed a definite 'EOAE'.

In the adults the mean measurement time amounted to 66 seconds (range 60 to 150 s) per ear.

In figure 2, the stimulus levels measured in the ear canal of both newborns and adults are shown in a histogram. These levels ranged from 0 to 96 dBSPL in the newborns, and from 80 to 96 dBSPL in the adults.

The artefact-rejection level was adjusted between 44 and 55 dBSPL in the newborns (mean 49 dBSPL), and between 43 and 50 dBSPL in the adults (mean 46 dBSPL).

The stability of the stimulus is shown in figure 3 and ranged from 0 to 100% in the newborns. In 85% of these cases the stability is over 70%. In the adults the stability of the stimulus shows the same range as in the newborns. However, in 95% of the ears tested, the stability is over 70%.

BASIC FEATURES

In the newborn ears the 'Echo'-levels ranged from 1.6 to 38.6 dBSPL (mean 20.2 dBSPL), the response reproducibilities ('Repro') from -29 to 99%. Ninety percent of the measurements had a reproducibility of 55% or higher. In the adult ears the response levels ranged from 2.7 to 20.6 dBSPL (mean 12.8 dBSPL), the response reproducibilities from 26 to 98%.

Figure 4 shows the response level plotted against the absolute reproducibility of the response for newborns and for adults. These two objective figures appear to be positively related, but for newborns and adults differently. The 2 lines in figure 4 represent an exponential function fitted by eye to the relation between the variables in the two groups separately.

The background noise level varied between 1.8 and 21.2 dBSPL (mean 7.8 dBSPL), and between -1.4 and 9.4 dBSPL (mean 1.5 dBSPL) in newborns and adults respectively.

Figure 5A shows a plot of the response level in newborns and in adults. In the newborns the response level is plotted against age at testing. Every ear is represented by a dot, a triangle or a circle. These symbols reflect our visual scores: 'EOAE' present, 'doubtful EOAE', and 'no EOAE', respectively. Also in figure 5A the 10, 50 and 90 percentile lines of the response level are shown. Figure 5B shows a relative histogram of the age at testing of the newborns. Figure 5C shows a relative histogram for the response level as recorded in adults and in newborns. The mode of the response level distribution for adults is at 15 to 20 dBSPL, at 20 to 25 dBSPL for newborns.

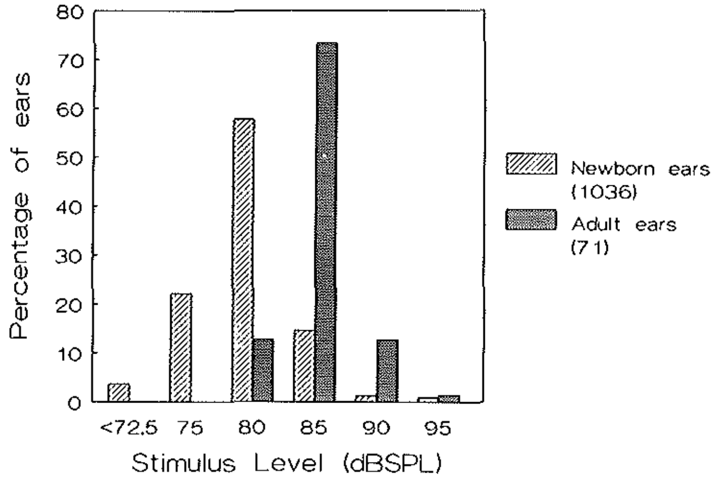


Figure 2
Relative histogram of the stimulus levels present during the EOAE recording in newborn and in adult ears. The remainder group of stimulus levels below 72.5 dBSPL is not representative of the actual level during the measurement (see discussion).

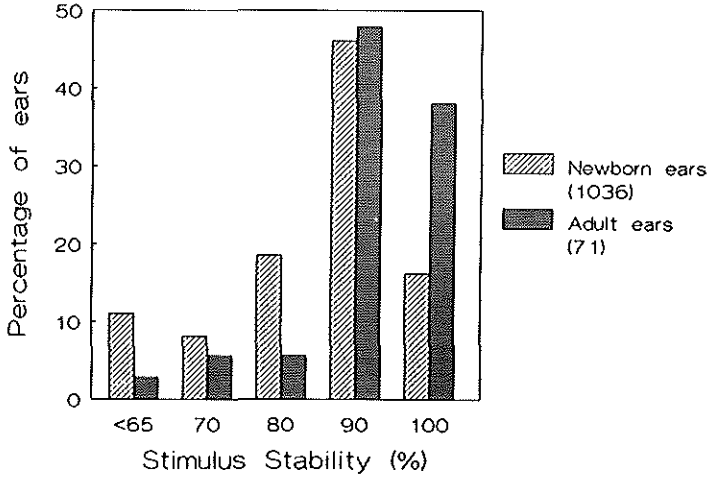


Figure 3
Relative histogram of the stability of the stimulus waveform during the EOAE recording in newborn and in adult ears. The remainder group of stimulus stabilities below 65% is not representative of the actual stimulus stability during the measurement (see discussion).

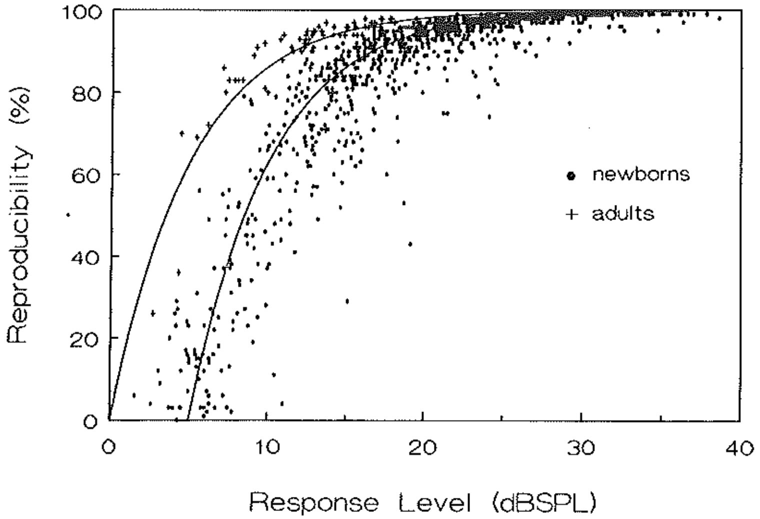


Figure 4

A plot of the absolute reproducibility against the level of the response for newborn as well as for adult ears, which are represented by 'dots' and 'plus signs' respectively. Solid lines are fitted by eye and describe the theoretical relation for responses with a normal amplitude distribution.

***Table 2:** The percentages of EOAE prevalence in different age groups of newborns and in adults.*

	Newborn ears					Adult ears
age: number of ears:	<36 h 140	36 - 72 h 523	72 - 108 h 236	≥108 h 137	total 1036	total 71
EOAE present	78	95.4	94.5	99.0	93.4	97.2
doubtful EOAE	4	1.6	0.5	1.0	1.3	2.8
no EOAE	18	3.4	5.0	0.0	5.3	0

PREVALENCE

According to our visual scores of the EOAE recordings in newborns (table 2), in 93.4% of all the ears tested an EOAE could be identified. In 5.3% of the newborn ears there was 'no EOAE' present, while in 1.3% there was 'a doubtful EOAE'.

Table 2 also shows the percentages of EOAE prevalence in different age groups. The prevalence of EOAEs appears to be age dependent. It is only 78% in 140 ears of healthy newborns younger than 36 hours, and 99.0% in 137 ears of newborns older than 108 hours of age. There is no such relation between the EOAE prevalence and the gestational age of the infants.

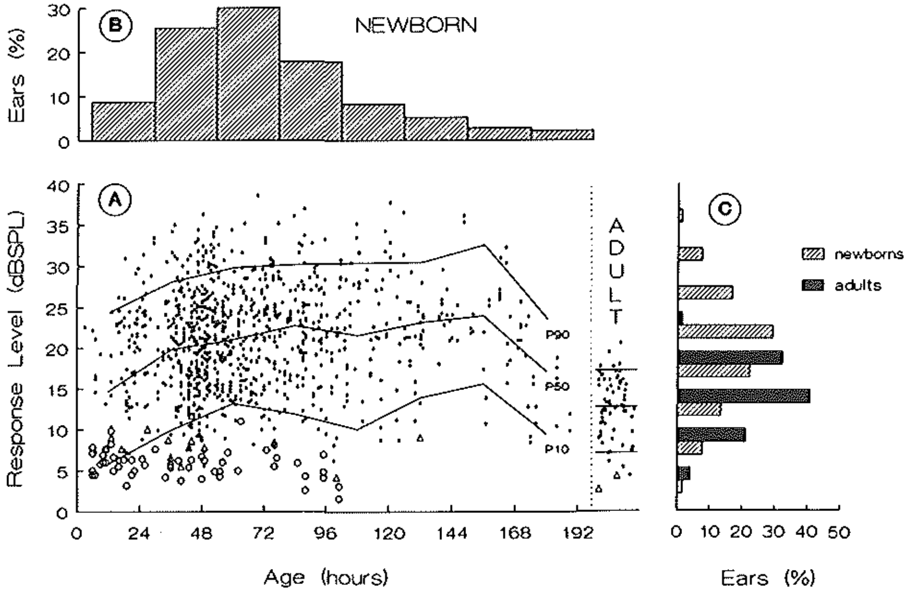


Figure 5

A A plot of the response level in newborns and in adults. In the newborns the response level is plotted against age. The visual scores, 'EOAE' present, 'a doubtful EOAE' and 'no EOAE' are represented by a dot, a triangle and a circle respectively. The 10, 50, and 90 percentile values of the response level are shown by solid lines.

B Relative histogram of the ages in hours of the newborns at the time of testing. The percentages of ears per age class of 24 h are calculated.

C Relative histogram of the response levels found in ears of newborns and adults.

According to the visual scores of the EOAE recordings in adults (table 2), in 97.2% of all the ears tested, an EOAE could be identified. In 2.8% of the ears 'a doubtful EOAE' existed. No ears with a visual score of 'no EOAE' were found.

DISCUSSION

FEASIBILITY

In most newborn ears the examination could be done easily. Only 4% had to be retested, because of restlessness at the first examination. The measurement duration was up to 7 minutes for 80% of the ears tested. This is clearly longer then a 1 to 2 minutes measurement time in cooperative adults, but acceptable for screening purposes.

Details about the measurement conditions are reflected by the test parameters. The stimulus level measured in the ear canal ranged from 0 to 96 dBSPL in the newborns. The histogram of figure 2 shows that in 36 ears the stimulus level displayed after the EOAE measurement was below 72.5 dBSPL. At the lower stimulation levels the EOAE-amplitude is linear with the stimulus amplitude *(Wit and Ritsma, 1979; Rutten, 1980; Grandori, 1985)*. Therefore, it would be possible that the (linear) EOAE was cancelled by the nonlinear differential stimulus method used by the ILO88 at low stimulation levels. But in our study, responses at such a low stimulus level were only accepted for inclusion if an EOAE was judged to be present. Otherwise the ear had to be retested, because the stimulus level had not been satisfactory. Explanation of the seemingly impossible presence of an EOAE after stimulation at extremely low levels (0 dBSPL), requires a technical note. The ILO88 calculates the peak sound pressure level of the stimulus at the moment the test is terminated. In a number of examinations the earphone and/or microphone canal in the probe became obliterated, or the probe fell out of the ear canal. The stimulus level then displayed is not representative of the actual level during the measurement, but (much) lower. The EOAE acquired up till the 'accidental' end of the recording, was still useful. In the adult ears the stimulus level varied between 80 and 96 dBSPL. The lack of extremely low stimulus levels in this group reflects the difference in ease of EOAE recording between the two groups.

In the newborns 22 responses have a stimulus level higher than 87 dBSPL. In 13 responses with an EOAE present, this is caused by movements of the newborn at the moment the test is terminated and the corrupted stimulus waveform was quantified by the ILO88. In the adults 10 ears have a stimulus level higher than 87 dBSPL, all stimulus waveforms are oscillatory due to unknown factors.

The mean artefact-rejection level in the newborns was 49 dBSPL, which is higher than the value of 46 dBSPL in the cooperative adult.

The stimulus stability was over 70% in 85% of the newborn ears tested. Of course the stability was especially low in these cases where the stimulus waveform was corrupted by infant movements, and in cases which showed a final stimulus level close to 0 dBSPL. In the 95% of the adult ears, the stability was over 70%. No retest attempt was made because of a poor stimulus stability in case of a clearly present EOAE in the averaged response.

BASIC FEATURES

Figure 4 shows the different relations between the response level and the reproducibility in newborns and adults. In both groups these two objective figures are positively related. The solid lines fitted by eye follow the relation [$\text{Repro}=(1-\exp(-0.2*(\text{level}-L_0)))$]. This formula describes the exact relation between the level (in dB) of the average of two responses and their correlation coefficient if the amplitude distributions of both responses are normal, have a zero mean, and equal variances *(Kreyszig, 1970)*. The values used for L_0 are 0 and 5 dBSPL for adults and newborns respectively. At a constant reproducibility newborns show on average a higher response level. Apparently, newborn recordings show a higher background noise. Indeed the difference between the means of the background noise in newborns and adults we found was 6.3 dBSPL, which compares favourably with the L_0-difference discussed

above. We think that the higher background noise level in newborns is caused by the use of a smaller probe, one that is more sensitive to environmental noise.
Compared with adults, the response level in the newborn ears is on average higher and the range is wider (figure 5C). In the newborns the response level ranged from 1.6 to 38.6 dBSPL (mean 20.2 dBSPL), and in the adults from 2.7 to 20.6 dBSPL (mean 12.8 dBSPL). The wider range of the response level in newborns compared with adults may partly be due to age effects, discussed below. Regarding the higher response levels in newborns, Bray and Kemp *(1987)* suggested that a reason for this may be the smaller ear canal volume. However, in our opinion, the higher response levels in newborns can also partly be explained by the frequent occurrence of strong Spontaneous Oto-Acoustic Emissions *(Wit et al, 1981; Chapter 2)*. The prevalence of SOAEs in normal hearing adult ears is reported to be 25 to 30% *(Fritze, 1983; Wier, 1984; Kemp et al, 1986; Cianfrone, 1986; Probst et al, 1987)*, while Bonfils et al *(1989)* reported a prevalence of 68% in infants younger than 18 months of age.

PREVALENCE

The presence of EOAEs was tested in 1036 ears of healthy newborns. Visually scored clear EOAEs were found in 93.4% of all ears (table 2), 'no EOAEs' in 5.3%. The remaining ears, 1.3%, showed 'a doubtful EOAE'. Our method of subjective scoring is rather tolerant, as we also scored 'EOAE-present' for those infrequent responses of which only part of the waveform is reproduced and the spectrum shows only a few narrow bands rising above the background noise. Given the current knowledge on the relation between the spectrum of the EOAE and the audiogram, we feel that at this moment it cannot be concluded that the audiogram is abnormal if the EOAE-spectrum is narrowband in character.

Although no proof has been given yet in the newborn group, one might accept EOAE presence as a proof of (near) normal ear function in the mid-frequencies *(Kemp et al, 1986; Collet et al, 1989)*. Then in this study 5.3% failed the EOAE screen. The prevalence of severe bilateral sensorineural hearing impairment in healthy newborns is 0.05-0.10% *(Schein and Delk, 1974; Martin et al, 1979)*. The prevalence of mild uni-/bilateral hearing loss in newborns is unknown. Also the prevalence of mild conductive losses in this group is unknown. As the prevalence of any form of hearing loss is only 0.37% in a population of Scandinavian children *(Kankkunen, 1982)*, we presume that our overall failure rate of 5.3% is mainly caused by middle ear dysfunction. Our data also suggest this cause, because the responses of the 'no EOAE' group show a significantly stronger stimulus level ($p<0.001$) then those of the 'EOAE' group. Previously, Mortensen and Mauk *(1991)* reported higher stimulus levels to be related to lower rates of EOAEs. A higher stimulus level in a subgroup of ears indicates a higher reflectance of the middle ear, given the constant electrical input to the earphone and the limited age range of the total group. Fluid in the middle ear is a plausible cause of this higher reflectance. Another difference between the 'no EOAE' and the 'EOAE' present group is that the age in hours of the newborns with an ear belonging to the 'no EOAE' group is significantly lower. Regarding this age effect on the prevalence in the total group, in 20 ears of 15 newborns the EOAE measurement was performed twice with a time interval of at least one day. The results, presented elsewhere *(Chapter 2)*, showed that the response grows stronger in the first days post partum. The speed of growth varies strongly between ears. We think that the EOAE prevalence is age dependent, due to changes in the middle ear function shortly after birth, when the middle ear must be cleared of (amniotic)fluid. From the viewpoint of the screening purpose of EOAE recordings we conclude that newborns should not be examined before the age of 4 days.

Recently also Marco et al *(1991)* reported EOAEs to be less prevalent in infants younger than one day of age compared with those older than 3 days of age.

The prevalence of EOAEs in the 71 normal adult ears was 97.2%. This value is equal to the EOAE prevalence in the newborns older than 3 to 4 days of age.

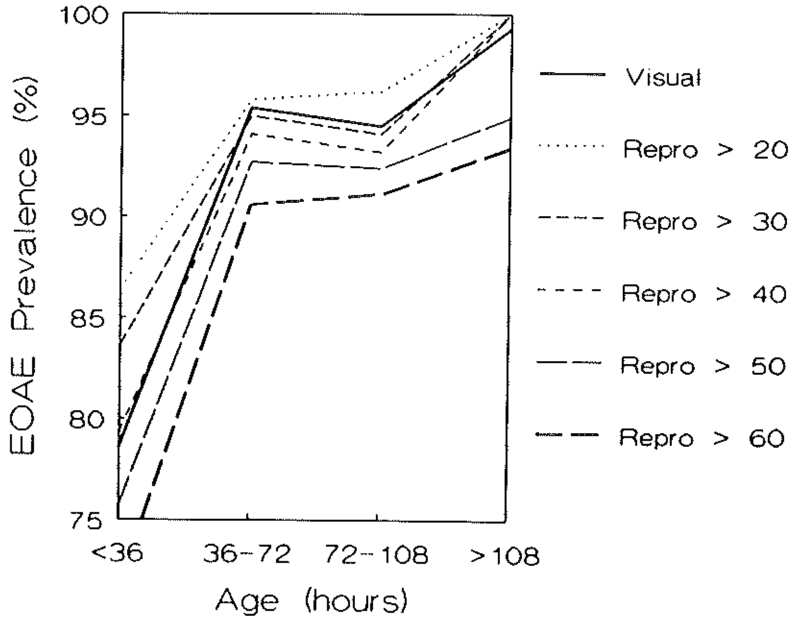


Figure 6

EOAE prevalence scores in different age groups of newborns. The prevalence according to our visual scoring is compared with the prevalence using the objective 'Repro' in detecting the presence of an EOAE.

Although in this study the presence of an EOAE was identified by visual scoring, we looked for an automatic scoring method. From the three objective variables ("Echo", "Repro", and "A-B"), the reproducibility is our first choice as the detection variable. For various criterion-values of this variable, we calculated the prevalence of EOAEs for different age groups (figure 6). We also plotted in this figure the subjectively-scored EOAE-prevalence, as listed in table 2. For both objective and subjective scoring, figure 6 shows that the EOAE prevalence increases with age. And as one might expect, in each age group the objectively scored prevalence decreases when the 'Repro' criterion is raised from 20 to 60%. When using the 'Repro' criterion of 20 and 30%, the EOAE prevalence is higher than according to our visual scores, especially for the lower age groups. When we use a 'Repro'-criterion as high as 50 and 60%, the EOAE prevalence is underestimated compared with the visual scoring. Overall the prevalence-age relation for the visual score (table 2, figure 6) is very similar to that of the objective score. Both scores closely agree on the prevalence-age relation for a reproducibility of about 40%. We found that with a criterion of 50% no ears pass the objective EOAE screen that failed the subjective visual screen. And using this criterion only 3.6% of the subjective passes failed the objective screen. So, 50% is a safe criterion in the sense that all failures are detected and the false alarm rate is low. Until a mass-examination of combined ABR and EOAE is available, reliable values for specificity are lacking. A similar analysis of a large number of impaired ears in newborns has to be done to determine the sensitivity of the EOAE-screen.

CONCLUSION

We conclude that:

1- EOAE screening in newborns can be done in a separate, but not silent room in the obstetric department.

2- The prevalence of EOAEs in healthy newborn ears is age related. It rises from 78% in ears of newborns younger than 36 hours of age to 99% in ears of newborns older than 108 hours of age.

3- The age effect on EOAE prevalence in newborns is probably related to the middle ear clearance of amniotic fluid.

4- The reproducibility of the response might serve as an objective EOAE detection variable for mass-screening. We propose a criterion of about 50%.

CHAPTER 4

THE POSTNATAL GROWTH PERIOD OF THE CLICK-EVOKED OTO-ACOUSTIC EMISSION IN HEALTHY NEWBORNS

ABSTRACT

Click-Evoked Oto-Acoustic Emission (EOAE) recording becomes more and more accepted as a method of ear function screening in newborns. In an earlier preliminary report we described the growth of the level of the EOAE the first days post partum *(Chapter 2)*. As the EOAE level and prevalence are related, this finding implies that screening should not be done too soon. The former growth figures were based on two recordings per infant at least separated by one day. In this study we report on the EOAE phenomenon following daily recordings in the first week of life.

Twelve healthy newborns were daily examined bilaterally with EOAE recording. The infants were successfully tested between 3 and 8 times (mean 6). For analyses age classes from 0 to 7 days post partum were formed. Parameters influencing the EOAE recording feasibility, i.e. stimulus level, artefact rejection level and stimulus stability were comparable for all age classes. The response parameters appear to change predominantly from day 0 to day 2. The response level and reproducibility increase, as the background noise level decreases. The visual EOAE prevalence is also increasing with age, from 50% at day 0, and 88% at day 1, to 100% at day 2 and higher.

Per ear the response level data with age were fitted with a simple saturating exponential growth function. Using this function there appears to be no relation between growth period of the response level and the final level. Within infants the left-right ear correlations for both the growth period and the final response level are high. The age at which the response level reaches at least 95% of the final value is 2 days in 50% and 5 days in 80% of the ears tested.

We conclude that EOAE screening in newborns should preferably not be done before the age of 2 to 4 days.

INTRODUCTION

In 1978 Kemp discovered the click-Evoked Oto-Acoustic Emission (EOAE). This phenomenon of cochlear origin can be recorded in 96-100% of the ears of healthy newborns *(Johnsen and Elberling, 1983; Elberling et al, 1985; Stevens et al, 1987; Bonfils et al, 1988a, 1990; Johnsen et al, 1988; Chapter 3)*. In normal hearing adult ears the same figures on EOAE prevalence are reported, but no EOAE can be recorded in an ear with a hearing loss exceeding 15-40 dB *(Kemp, 1978; Rutten, 1980; Probst et al, 1987; Bonfils et al, 1988a,b; Stevens et al, 1988; Dolhen and Chantry, 1988b; Collet et al 1989; Lutman, 1989; Prieve et al, 1993)*. Reports comparing EOAE and Brainstem Electric Response Audiometry (BERA) results suggest a comparable relation between presence of EOAEs and hearing loss in newborns *(Bonfils et al, 1988a,b; Stevens et al, 1990)* as found in adults.

These findings and the fact that EOAE recording is objective and can be done more easily than other objective methods lead to the suggestion of using EOAEs to screen for ear function in newborns.

To evaluate the possibility of screening healthy newborns by EOAE recording we started a study in about 1000 ears. Soon we noticed that the average EOAE level appeared less strong in newborns tested directly post partum compared to the level in newborns tested a few days later. In an earlier paper based on two EOAE recordings per ear at least one day apart in 20 ears *(Chapter 2)* we reported our finding of growth of the EOAE strength. In an other study *(Chapter 3)* we reported on the growth of the EOAE prevalence of the EOAE in the first days post partum. We concluded that an unnecessarily high false alarm rate would result when screening is done too soon after birth. As the postnatal growth of the EOAE strength seems the underlying cause for the growth of EOAE prevalence with age in the first week of life we carried out this longitudinal study in 24 ears, which aims at describing the postnatal growth of the EOAE in more detail.

MATERIAL AND METHODS

SUBJECTS

EOAEs were recorded daily in 24 ears of 12 healthy newborns (8 boys; 4 girls) in the first week of life. Eleven of these infants were born by (elective) sectio cesarian. The practical reason for including these healthy newborns is that they remained hospitalized with their mother. The twelfth infant was born after a normal delivery, but stayed in hospital with the mother on a social indication. At the first recording session the age of the newborns varied between 1 and 31 hours (mean 13 h). At birth the gestational age of the infants varied between 36 and 41 weeks, while their weights were between 2640 and 4345 g.

EQUIPMENT

The at the time only commercially available equipment was used in its default setting (ILO88, Otodynamics London, UK, software Version 3.0). This equipment was described previously in more detail elsewhere *(Kemp et al, 1990; Chapter 3)*. The first version of the 'newborn probe' was used and sealed into the ear canal using rubber or silicon tubing. After a good seal had been reached, the ear was stimulated with a click. During response acquisition artefact-rejection was applied, the level of which could be manually adjusted by the tester. The artefact rejection level was adapted to the recording conditions for each ear. The non-linear component of the otoacoustic response was averaged out of 260 accepted sweeps in two subaverages of 130 sweeps over the 2.5-20 ms poststimulus time interval. The instrument calculated and displayed a set of numerical data pertaining to each recording. The peak-to-peak sound pressure level of the stimulus is calculated by the ILO88. The stability of the probe fit during the recording is calculated by the stability of the stimulus waveform. The response level, background noise level, and the reproducibility, i.e. the correlation coefficient between the two subaverage waveforms, are calculated too. The spectra of the response and the background noise are displayed.

PROCEDURES

EOAE recordings in the newborns were made at the well baby ward in a separate but not sound treated room. The examinations were done in the presence of the mother in most cases. A recording was rejected for further analysis if the stimulus level had been below 78 dBSPL and the response did not show an EOAE. When this happened a second recording attempt was done immediately. Each day one recording session per infant was done.

DATA PROCESSING

The age at the time of testing was recorded in hours and recoded to a decimal number of days (age in hours divided by 24). For some analyses this age was rounded to an integer value, which results in age classes of one day, covering the range of day 0 to day 7 post partum.

The following standardly available quantitative measures of the stimulus and the response were used: the level of the stimulus (displayed on the ILO88 as 'Peak'), the applied artefact-rejection criterion ('Peaklimit'), the stability of the stimulus ('Stabil'), the response level ('Echo'), the reproducibility of the response ('Repro'), and the background noise level ('A-B').

For the (statistical) analyses of the data we used SPSS Release 4.0.

Nonlinear regression analysis

The growth in response level with age for each ear was analyzed with a mathematical function. Assuming that the response level would saturate eventually, the data points were first fitted using a negative exponential growth function with 3 parameters.

Growth function:

$$\text{response level} = L * (1 - e^{(c - t)/\tau}) \quad [1]$$

L symbolizes the final response level, t is the age at the time of the recording. The parameter c indicates the age of onset of the response. τ is the time constant of growth. This parameter represents the speed of growth of the response level, the constant is high if the speed of

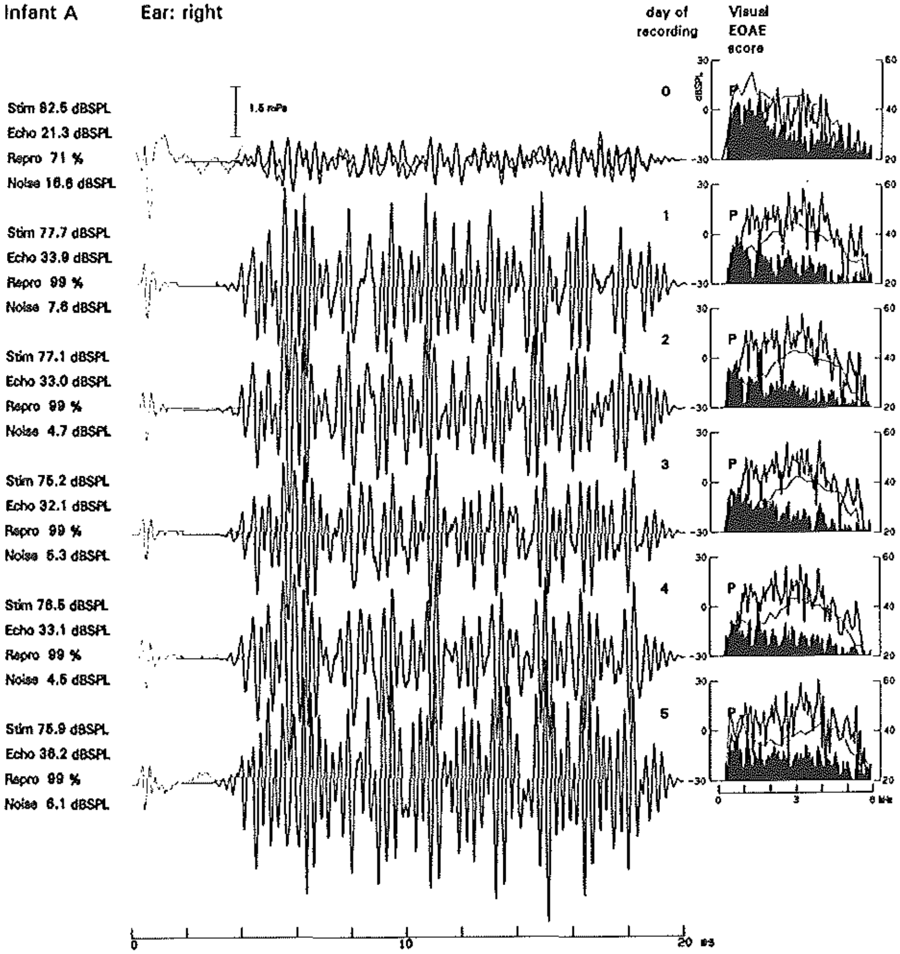


Figure 1A

The results of EOAE recordings made in a newborn in the first week of life. An EOAE was already present in both ears from the first test occasion, i.e. day 0.

The response waveforms, consisting of A and B trace are shown, vertically sorted by the age in days of the infant at the time of the recording. The dashed line at the beginning of the recorded waveform is the stimulus waveform. Above the total waveform to the right the age in days post partum is given. In front of the waveform the stimulus level ('Stim'), response level ('Echo'), response reproducibility ('Repro'), and background noise level ('Noise') are shown. Behind the waveform the spectrum of the response and background noise are displayed, in white and black respectively, and related to the left Y-axis in dBSPL. The dashed line in the spectrum represents the stimulus spectrum, which is related to the dashed right Y-axis in dBSPL. The visual EOAE score is displayed above the spectrum; 'A' for an absent EOAE, 'D' for a doubtful EOAE or 'P' for a present EOAE in the response.

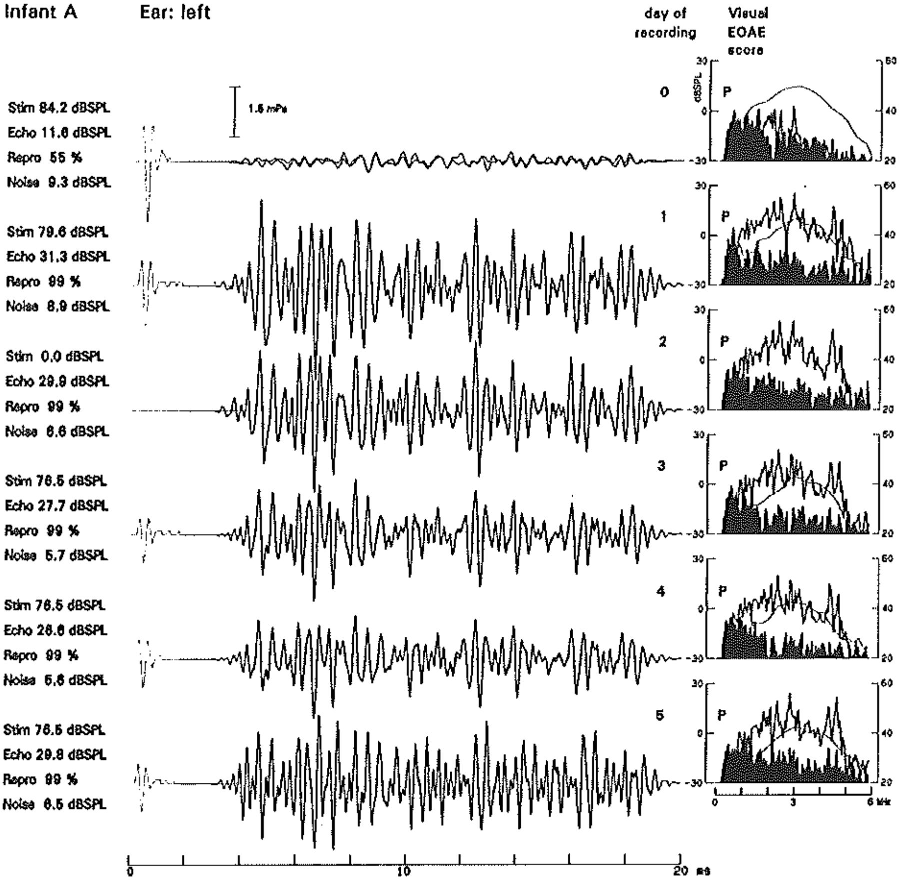


Figure 1B
The results of EOAE recordings made in a newborn in the first week of life.

growth is low. Since the growth of the EOAE level must have started at some point in time, we estimated the age at which the response level would have been 0 dBSPL by averaging the c-values resulting from the 23 successful (= converging) curve fits. This value was -0.7 days. As we were mainly interested in the time constant of growth and the final response level after about one week, we fitted the response level data with a simpler growth function [2] with these two parameters only, while the response level was forced to be 0 dBSPL at the age of -0.7 days.

$$\text{response level} = L * \left(1 - e^{(-0.7-t)/\tau}\right) \quad [2]$$

Using this growth function we were able to fit the response level data in 23 ears with an error of estimate of 1.4 dB (range 0.4 to 3.7 dB) per ear.

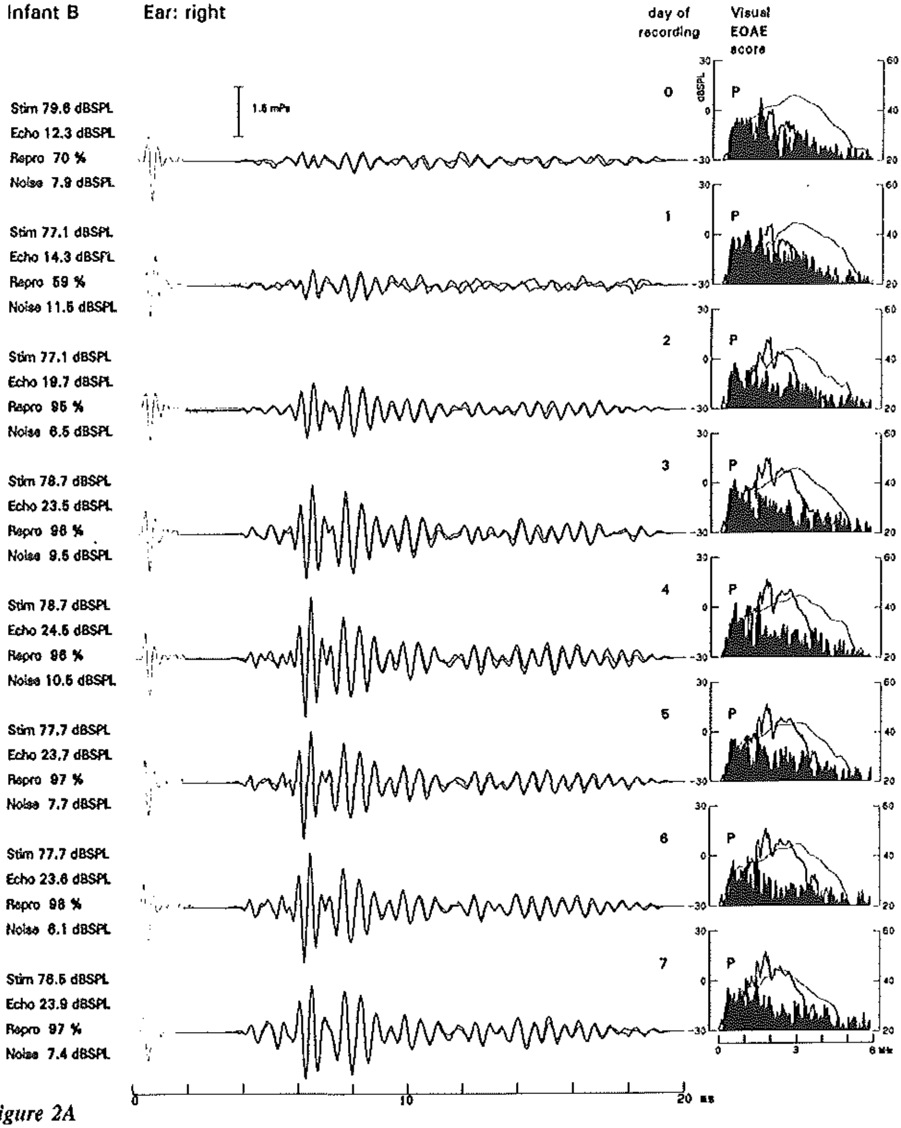


Figure 2A

The results of EOAE recordings made in a newborn in the first week of life. An EOAE was present from day 0 in the right ear (see the legend of figure 1A for explanation).

Visual response scoring

The presence, doubtful presence or absence of an EOAE in the response waveform was scored visually *(Chapter 3)*. This subjective score was based on the response waveform, the reproducibility of the response and the strength of the response spectrum relative to that of the background noise.

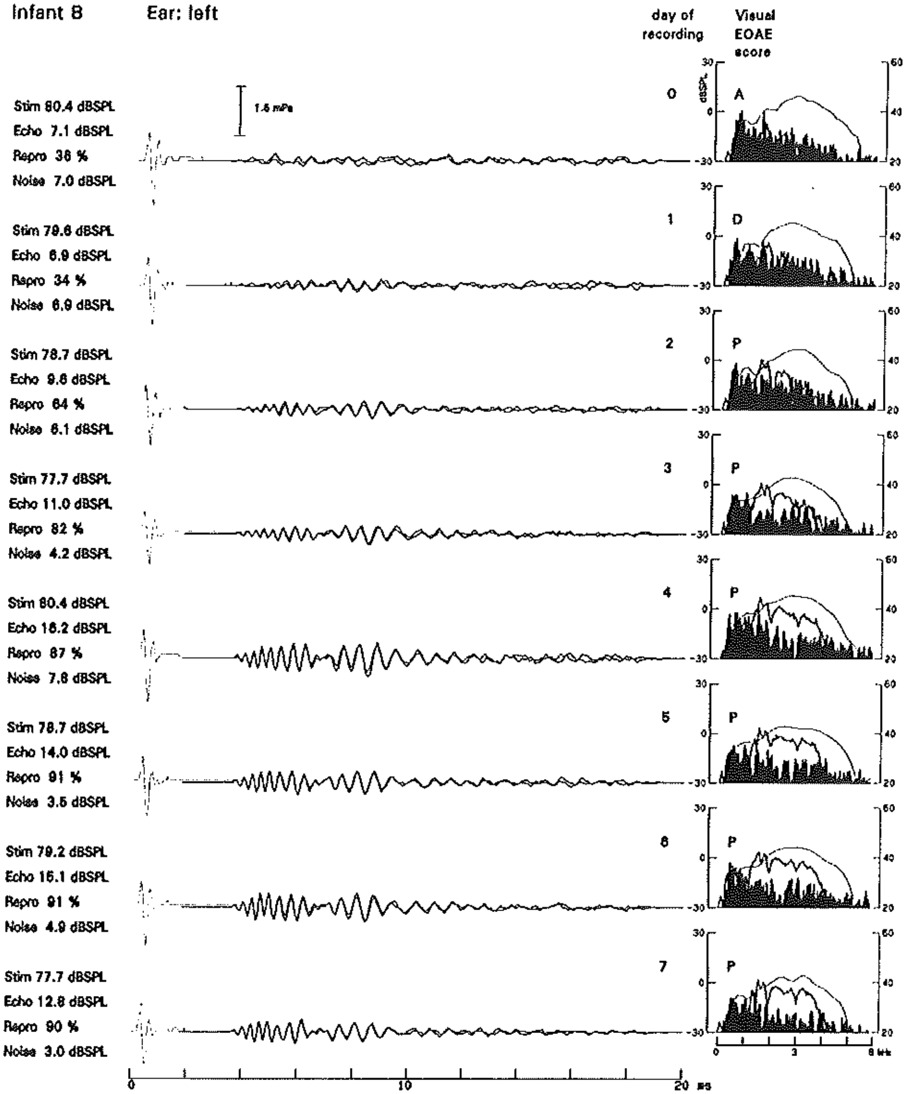


Figure 2B

The left ear showed 'no EOAE' at day 0, 'a doubtful EOAE' at day 1 and a clear EOAE in the recordings made on the following days.

RESULTS

We observed large intra-individual variations in the growth period of the EOAE. Examples of the recording results in both ears of two infants in the first week post partum are shown in figure 1 and 2, infant A and B respectively.

In the ears of infant A (figure 1) an EOAE was already present bilaterally at the first test occasion at day 0 after birth. Both the response level and reproducibility increased significantly from day 0 to 1. In infant B (figure 2) an EOAE was also present at day 0 in the right ear, but the response level and reproducibility kept growing for about three days. 'No EOAE' was present at day 0 in the left ear of this infant, a 'doubtful EOAE' at day 1, and a clear EOAE was present in the recordings made on the following days. However, both the response level and the reproducibility appeared to keep increasing up to day 4. The final response level as well as the growth period appeared to vary strongly between infants, and less between the left and the right ear within infants. The inter-day intra-ear waveform stability as judged by eye was high once an EOAE was present.

Table 1: Number of ears tested with EOAE recording 0 to 7 days post partum, with median values of the response level and reproducibility, and the background noise level, and with the percentage of EOAE prevalence.

day(s) post partum	0	1	2	3	4	5	6	7
number of ears	14	24	24	24	19	20	10	12
median response level (dBSPL)	10.9	14.7	18.0	19.1	18.9	18.2	19.4	20.5
median reproducibility (%)	46	86	91	92	95	95	95	96
median background noise level (dBSPL)	8.0	6.9	6.7	6.2	6.0	6.5	6.4	5.5
visually scored EOAE prevalence (%)	50	88	100	100	100	100	100	100

We were able to examine the infants between 3 and 8 times (mean 6). Table 1 shows the number of ears tested at day 0 through 7. Five newborns were not tested at day 0, for the practical reason that they had not been transferred from the OR/delivery room to the obstetric department yet, at the time of the day that testing was normally done. Two infants went home with their mother at day 4, another infant at day 6, and we stopped testing at day 7. We were unsuccessful in testing one ear at day 4 of one infant, and in two ears at day 6 of another infant, because of restlessness of the newborns. Overall 147 recordings were done in the 24 ears.

Figure 3 shows a plot of the reproducibility of each response against its level for all recordings done from day 0 to 7. The solid line shows the theoretical relation between reproducibility and response level fitted on the data of 1036 ears of healthy newborns *(Chapter 3)*. It is clear that the data points at day 0 (open circles) are predominantly located around the lower part of the curve. At day 1 (open squares) they are already spread over the

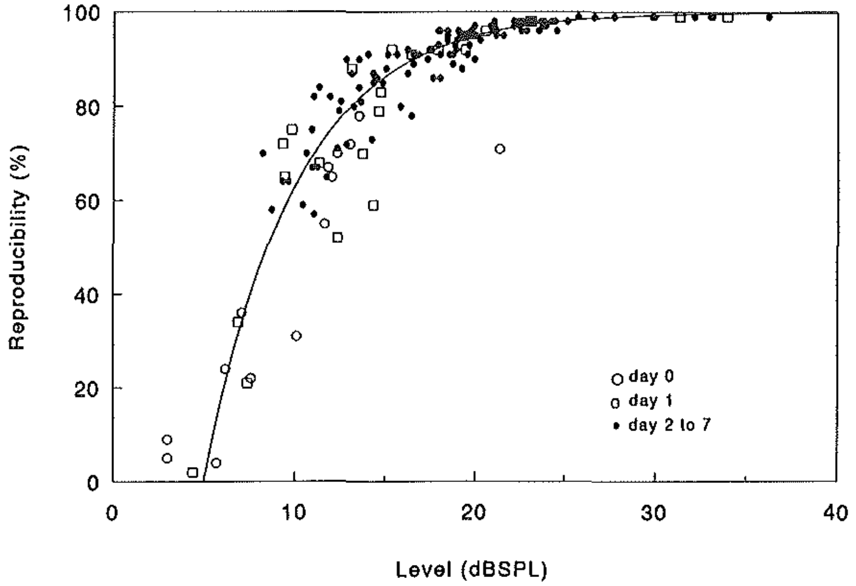


Figure 3
A plot of the reproducibility of the response against its level for all recordings. The day 0 and day 1 recordings are represented by open circles and squares respectively. From day 2 and up recordings are symbolized by dots. The solid line shows the theoretical relation between response reproducibility and response level fitted on the data of 1036 ears of healthy newborns (Chapter 3).

whole range of the curve and from day 2 on (black dots) they are located around the upper part of the curve. So, the level and the reproducibility of the response appear to grow stronger the first days post partum. This growth is different between ears and infants. The reproducibility and response level data points fitted rather well by the reproducibility-level relation curve.

Table 1 also shows the median values of the response level, the reproducibility and the background noise level per age class. The response level and reproducibility appear to increase with age, while the background noise level decreases.
Visually scored, an EOAE was present in 7 (50%) of the ears tested at day 0, 21 (88%) at day 1, and in every ear (100%) tested at day 2 and higher (table 1). Once an EOAE had been recorded in an ear for the first time, all following recordings showed an EOAE also.

The artefact-rejection level, the stimulus level and the stability of the stimulus of the recordings were comparable to the figures found in the cross-sectional study in over 1000 ears of healthy newborns in the first week of life *(Chapter 3)*.

DISCUSSION

The aim of this study was to follow the EOAE phenomenon daily in the first week post partum in 12 newborns. We made these recordings predominantly in infants born by elective sectio cesarian as these are healthy newborns who remained hospitalized with their mother for 4 to 8 days post partum. Only 3 (2%) of all recording attempts were unsuccessful at the end of one test session per day.

Considering the results of bilateral EOAE recording in two newborns in the first week of life (figure 1 and 2), it is clear that EOAE features vary strongly between infants, and less between right and left ears within infants. Once a clear EOAE was recorded in a newborn ear shortly after birth, the stability of the EOAE waveform as judged by eye remained high. This was previously reported for adults *(Kemp, 1982; Grandori, 1983).*

In figure 3 the response reproducibility is plotted against its level for all recordings. The recordings done at day 0 are represented by open circles, at day 1 by open squares. The recordings done at day 2 and higher are given by dots. These daily data are projected on the theoretical response reproducibility-level relation derived by the fitting on such data from 1036 ears of healthy newborns. As can be seen in this figure, only at day 0 and 1 data points are found around the lower part of the curve. These recordings showed a low response level and a reproducibility below 50%. As a reproducibility of 50% has been suggested as an objective EOAE criterion these responses would get the score 'absent EOAE' *(Chapter 3).* From day 2 on, data points are all above 50% reproducibility, which is in accordance with the 100% visual EOAE prevalence found.

In spite of the different way of delivery, i.e. sectio cesarian versus natural, the increase in EOAE prevalence in this study is in agreement with our findings in 1036 ears of healthy newborns *(Chapter 3).* This indicates that absence of an EOAE immediately post partum is not directly related to the (generally) more stressful character of the natural delivery.

In short, EOAE features predominantly changed from day 0 to day 2 after birth. The response level and reproducibility increased as the background noise level decreased. From day 2 on EOAE features were more or less stable.

Also considering the range and distribution of the artefact rejection level, the stimulus level and the stability of the stimulus, the recordings in this small group of newborns were comparable to those reported in our larger study. These parameters influencing the feasibility of EOAE recording did not change significantly between the recordings from day 0 to day 7.

A mathematical function was used to analyze the growth in response level with age for each ear. This function was based on the assumption that the response level will saturate eventually. Because one ear was examined only three times it had to be excluded from the analysis. It makes no sense to fit a curve with 2 free parameters and only 3 data points. In the other ears we succeeded in fitting the EOAE response level data the first days post partum with this simple negative-exponential function. The final response level for each ear is a parameter from the fitted function and varied between 10.0 and 34.3 dBSPL (mean 19.7 dBSPL). Although the variability of the final level was high, the intra-infant inter-ear correlation of this level was 0.65 and significant.

Figure 4 shows a histogram of the percentages of ears with a certain final response level, as well as a line diagram (dashed) of the cumulative percentages.

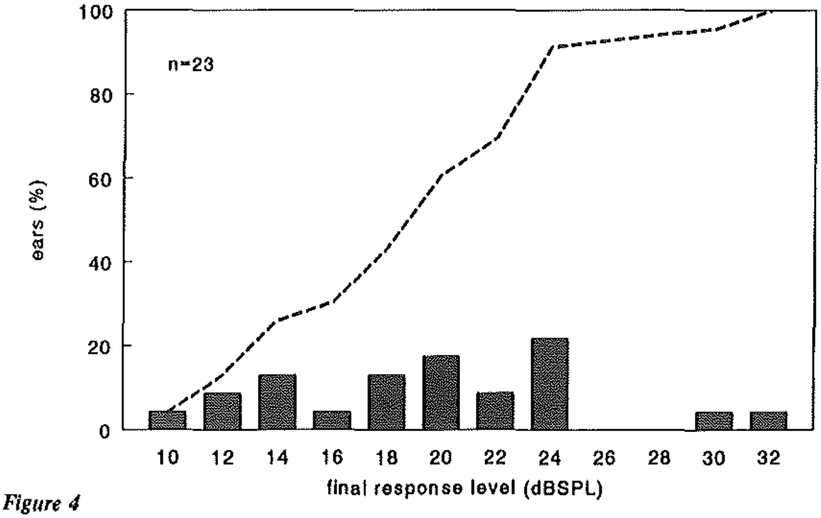


Figure 4

Relative histogram of the final response level. The dashed line shows the cumulative percentages.

We also calculated a growth period, the age in days (t_{95}) at which 95% of the final response level was reached. Figure 5 shows a histogram of the percentages of ears reaching this level each day, as well as a line diagram (dashed) of the cumulative percentages. t_{95} varied from -0.5 to 6.8 days post partum. Nearly 20% of the ears already reached the final level (almost) at the first recording on day 0. 50% of the ears had reached 95% of the final response level at day 2, 80% at day 5. The left-right ear correlation for the growth period was high.

There was no significant correlation between final response level and growth period of the EOAE.

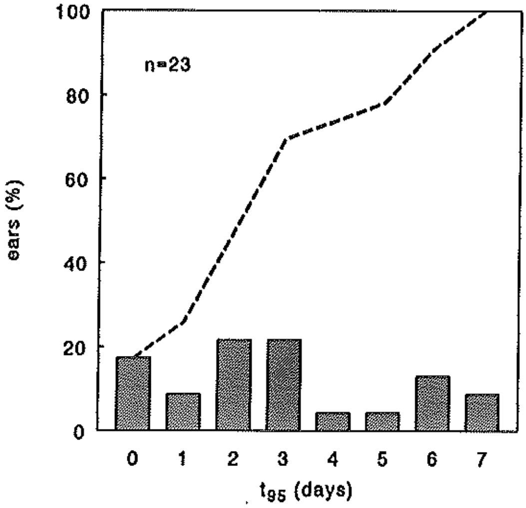


Figure 5
Relative histogram of t_{95}, i.e. the age in days at which 95% of the final response level is reached. The dashed line shows the cumulative percentages.

Concluding, although the manner of growth can be modelled similarly, the final response level as well as the postnatal growth period of the EOAE varied strongly between infants, while the two features were independent.

We think changes in EOAE features and prevalence were mainly caused by middle ear dysfunction, and debris in the ear canal the first days post partum. Mortensen and Mauk *(1991)* and we *(Chapter 2)* found a higher stimulus level in ears not showing an EOAE, which we found too in an earlier study. In the longitudinal study described in this paper there are not enough ears showing 'no EOAE' to repeat this finding. In the previous study we suggested fluid in the middle ear cavity as a plausible cause for a higher middle ear reflectance and concomitantly a higher stimulus level recorded in the ear canal.

CONCLUSION

The most important changes in EOAEs occur between day 0 and 2 after birth. The response level grows negative-exponentially with age to a saturation level. The growth period as well as the final level are very different between infants and somewhat less within infants. At day 5, 80% of the ears has reached 95% of the final response level. Although the growth in EOAE level is slow in a considerable number of cases, the final levels are generally high. Consequently, the EOAE is already detectable after a couple of days in a large proportion of infants *(Elberling et al, 1985; Stevens et al, 1987; Johnsen et al, 1988; Chapter 3)*.

CHAPTER 5

ASPECTS OF SPONTANEOUS OTO-ACOUSTIC EMISSIONS IN HEALTHY NEWBORNS

ABSTRACT

Spontaneous Oto-Acoustic Emissions (SOAEs) are pure-tone like signals, spontaneously present in the ear canal. In normal adult ears the prevalence of SOAEs is reported to be 30-70%, probably depending on the noise floor of the recordings. In infant studies, results on the SOAE prevalence are rare.

SOAEs as well as Evoked Oto-Acoustic Emissions (EOAEs) were recorded in healthy newborns. Their ages varied between 1 and 10 days. The recordings were done with commercially available equipment in a separate not sound treated room of the obstetric department. The prevalence of SOAEs was 78%, which is higher than previously reported for adults as well as healthy newborns. The prevalence was not significantly different between left and right ears, or genders. The number of emissions per emitting ear amounted on average 5.5. The median number of SOAEs in boys (3.3) is significantly lower than in girls (4.6). The SOAE levels were between -2 and 42 dBSPL. The mean level per emitting ear was 8.0 dBSPL and not significantly different between right and left ears or genders. However, the level of the strongest emission per emitting ear was significantly higher for right than for left ears. In contrast with adults most of the emissions (70%) are at frequencies above 2 kHz. Comparing the levels of the EOAEs between ears with and without SOAEs we found a statistically significant higher EOAE level in ears with SOAEs. This supports our previous hypothesis that the higher EOAE level found in healthy newborns is partly due to the more frequent presence of stronger SOAEs in healthy newborns.

Given these results in newborns and in view of the literature, we hypothesize that major developmental changes in the OAE phenomenon occur between 0 and 6 years of age.

INTRODUCTION

After Kemp *(1978)* discovered the phenomenon of Evoked Oto-Acoustic Emissions (EOAEs), some sounds spontaneously present in the ear canal appeared to have a cochlear origin *(Kemp, 1979; Zurek, 1981)*. The spectrum registered in the sealed ear canal without acoustic stimulation of the ear may show one or more pure-tone like signals, the Spontaneous Oto-Acoustic Emissions (SOAEs). SOAE frequencies are reported to be very stable over time, while their amplitudes may change. The implication of the presence of one or more SOAEs is still unclear. SOAEs appear not to be present in ears with 25 dB hearing loss or more *(Fritze, 1983; Probst et al, 1987)*, and Schloth *(1983)* reported that SOAE frequencies corresponded with sensitivity maxima in the microstructure of the audiogram. On the other hand, cases have been reported with cochlear hearing loss and SOAEs in the frequency range of the loss *(Glanville et al, 1971; Mathis et al, 1991)*.

In ears of normal hearing adults the prevalence of SOAEs is reported to be about 30%. In subjects the prevalence is about 40%, which proves that ears are not independent in having a SOAE *(Zurek, 1981; Fritze, 1983; Schloth, 1983; Wier, 1984; Kemp et al, 1986; Cianfrone, 1986;*

Probst et al, 1987; Rebillard et al, 1987). Lonsbury-Martin et al *(1990b)* reported a prevalence of 48%, and Zwicker *(1990)* even of 70%. The noise floor of the SOAE recordings appears to influence the SOAE-prevalence found *(Martin et al, 1990; Probst et al, 1991).* This noise floor depends on the equipment and the acoustical environment at test-time.

In infant and child studies, results on the SOAE prevalence seem rather inconsistent. Strickland and Burns *(1985)* find 26 to 31% of ears with SOAEs in children between 6 and 12 years. Bonfils et al *(1989)* report a SOAE prevalence of 68% in infants younger than 18 months of age, and Burns et al *(1992)* of 64% in neonates.

This paper describes the prevalence and other aspects of SOAEs in 176 newborn ears included in another study in over 1000 newborn ears. In this other study *(Chapter 3)* some aspects of the EOAE were studied as to ear function screening. We observed a higher mean EOAE level in newborns compared with adults. We hypothesized that the EOAE level difference between newborns and adults, is due to more prevalent and stronger SOAEs in the newborn. Real evidence may be provided by comparison of SOAE aspects and EOAE amplitudes in newborn ears with and without SOAEs. Therefore we recorded both the EOAE and the SOAE(s) in 176 consecutive newborn ears. More specifically this study aimed at answering the following questions:

1. What are the prevalence, levels, and frequencies of SOAEs in newborns?
2. How do these SOAE aspects in newborns differ from those in adults as reported in literature?
3. Is the presence of SOAEs related to the higher EOAE response level found in the newborn?

MATERIAL AND METHODS

SUBJECTS

EOAEs and SOAEs were recorded in 176 ears of 93 healthy newborns. In 10 infants we were unable to perform both recordings in both ears because of restlessness of the newborn at the first test occasion, and discharge from hospital before a second test session. 83 infants were successfully tested bilaterally. The newborns were included in the first days post partum, while staying at the obstetric ward. Infants scoring positively on the high risk register for hearing disability were excluded *(Joint Committee on Infant Hearing, 1983).* The age of the newborns at testing varied between 31 and 238 hours (mean 72 h). The gestational age of the infants varied between 36 and 43 weeks (mean 39 weeks), while their birth weights were between 2190 and 4345 gram (mean 3177 g). 99 of the ears were from boys (48 right; 51 left), and 77 from girls (38 right; 39 left). The age at the time of testing, the gestational age, and birth weight were statistically not significantly different between the sexes.

EQUIPMENT

For EOAE recording we used the ILO88 (Otodynamics, London, software Version 3.0) in its default settings *(Kemp et al, 1990; Chapter 3).*
For the SOAE recording we used the ILO88 in "mode 5". In this mode the final SOAE recording is a power spectrum averaged over ninety 6.250 kHz-wide FFT-frames with a frequency resolution of 12 Hz. In subsequent analysis we only used the frequency range between 1.050 and 6.250 kHz.
The SOAE recording was always preceded by the EOAE recording so the "check probe-fit" routine was executed. During the SOAE measurement there is no indication of the stability of the probe-fit, because the ILO88 needs a stimulus to quantify this stability. But a good fit is also reflected by a steady and minimal noise leakage into the meatus as indicated by the 'noise bar'. Therefore, during the measurement the artefact-rejection level, which can be manually adjusted was kept constant and as low as possible.

All recordings were done with the first version of the ILO88 newborn probe, one without specially designed disposable tips. It was sealed into the ear canal with a piece of a rubber or a silicon tube around the probe tip.

CALIBRATION

The strength of the SOAEs displayed by the ILO88 in mode 5 are given in arbitrary log-units. We calibrated the strength in dBSPL. As mode 5 of the ILO88 is rather poorly documented, more details on the calibration procedure are given in the appendix.

PROCEDURES

The EOAE and SOAE recordings in the newborns were made in a separate but not sound treated room of the obstetric ward. During the examinations the infants were lying in their cribs in various positions. Most of the infants were asleep, the others were quiet enough to test. In all cases first the EOAE recording was done, immediately followed by the SOAE recording. In most cases the mother was present during the examination.

DATA PROCESSING

Subjective EOAE score

The presence or absence of an EOAE in the response wave form was scored visually by the first and second author. The scoring is based on the response waveform, the reproducibility of the response waveform and the relative strength of the frequencies in the spectrum of the response, rising above the background noise. According to these visual scores, a response showed an 'EOAE', 'no EOAE', or a 'doubtful EOAE'. More details about our visual EOAE scoring method are discussed elsewhere *(Chapter 3).*

Objective EOAE variables

The level ('Echo') and reproducibility ('Repro') of each response were analyzed. The reproducibility is a Pearson coefficient of correlation between the test and retest waveform alternatingly acquired by the ILO88. An EOAE was scored to be present objectively if the reproducibility was over 40%. This reproducibility criterion was proposed in an earlier paper *(Chapter 3),* describing the prevalence-age relation of EOAEs in healthy newborns the first days post partum. The visual score and objective EOAE score appeared to agree closely on the prevalence-age relation.

SOAE scoring

The presence or absence of a spectral peak in the recorded power spectrum was detected automatically from the ILO88 data files with help of a custom-made computer program. The procedure is described in the appendix.

For each peak the frequency, the sound pressure level and the signal to noise ratio were determined. A spectral peak was accepted as signifying a definite 'SOAE' if the signal-to-noise ratio exceeded 4 dB, and as a 'probable SOAE' if between 3 and 4 dB. Spectra with peaks less than 3.0 dB above the noise floor obtained a 'no SOAE' score. Peaks at the frequencies 1147, 1428 and 1440 Hz are considered due to equipmental artifacts and were excluded from this analysis. Definite peaks could be recorded at 1147 Hz in a 2-cc test cavity. The source of this artefact is still unknown. Peaks at the frequencies 1428 and 1440 Hz were often detected and proven to be due to the equipment's ventilator noise.

RESULTS

EOAE RESULTS

Visual

The responses showed an 'EOAE' in 174 (98.9%) of the 176 ears of 93 consecutively tested newborns. In one ear 'no EOAE' was observed, and in another ear and subject, a 'doubtful EOAE'.

Objective

The response level ('Echo') in all ears tested varied between 6.2 and 37.0 dBSPL (mean 21.2 dBSPL), the response reproducibility between -2 and 99%. Taking 40% as criterion value *(Chapter 3),* the objective EOAE prevalence is 98.9%. The two ears that show no

EOAE based on this objective reproducibility-criterion are the same ears that did not get an 'EOAE' score visually.

SOAE RESULTS

In 137 (77.8%) of the 176 newborn ears tested, one or more SOAEs could be identified. Figure 1 shows some examples. In 22 ears (12.5%) 'no SOAE' was observed (figure 1), in 17 ears (9.7%) a 'doubtful SOAE'. The 2 ears that scored negatively on EOAE presence did score positively on SOAE presence.

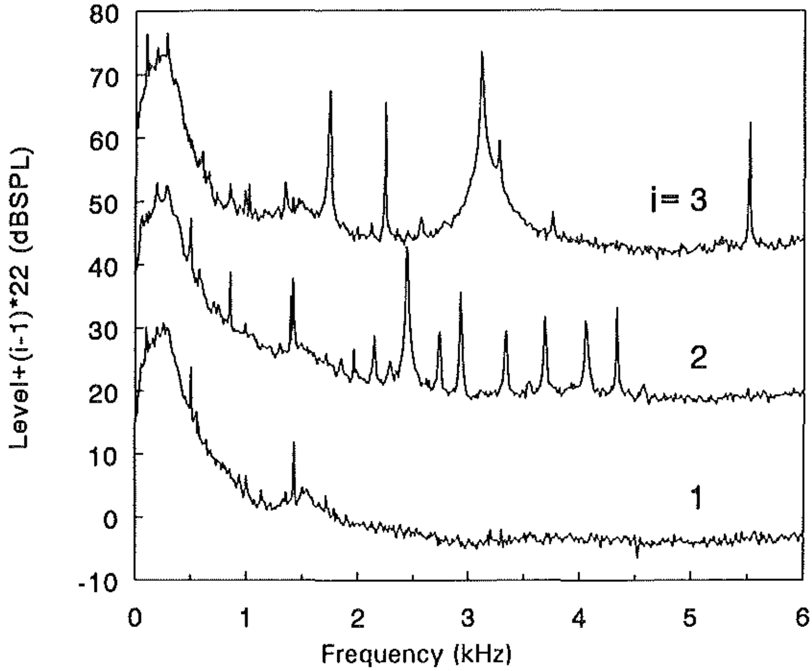


Figure 1

Three results of the SOAE recordings in healthy newborns. The spectral binwidth used was 1/81.92 kHz. Spectra were analyzed on SOAE presence in the frequency range from 1050 to 6250 Hz. In the spectra labelled 2 and 3, SOAEs were identified but not in the spectrum labelled 1. In that spectrum the only spectral peak that can be seen has a frequency of 1440 Hz, and is due to equipmental noise. The SOAE level in dB can be calculated by filling in the label number of the power spectrum in the equation along the Y-axis.

Table 1 shows the SOAE prevalence rates for all ears and separately for boys and girls. The SOAE prevalence in infants tested in both ears is given similarly.

Table 1: SOAE prevalence in ears and bilaterally tested infants.

SOAE prevalence in ears of healthy newborns (%)			
Ears (n)	Total (176)	Boys (99)	Girls (77)
in all ears	77.8	76.8	79.2
in R ears	83.7	79.2	89.5
in L ears	72.2	74.5	69.2

SOAE prevalence in newborns bilaterally tested (%)			
Newborns (n)	Total (83)	Boys (47)	Girls (36)
bilateral	67.4	65.9	69.4
in R ear only	18.1	12.8	25.0
in L ear only	7.2	10.6	2.7

R = right; L = left.

The SOAE prevalence tends to be higher in right than in left ears, but this difference is not significant (Mann-Whitney (M-W), p=0.07). We tested for significant differences between SOAE prevalence rates per ear for the factors side and gender, combined and separately. Only the SOAE prevalence for girls is significantly higher in right than in left ears (M-W, p=0.03).

In 83 of the 93 newborns, the SOAE recording was performed in both ears. In 77 of these 83 newborns (93%) SOAEs could be identified. In 56 (67%) of them SOAEs were present in both ears.

Restricting ourselves to the 'SOAE' present group of responses, a total of 751 SOAEs were found in 137 ears, on average 5.5 per ear. Figure 2 shows a cumulative distribution for the number of SOAEs per ear. This was done for boys and girls separately. The median number of SOAEs per ear in boys (3.3) is significantly lower than in girls (4.6) (M-W, p=0.04). This number is also lower for left than for right ears (M-W, p=0.02). We also tested the number of SOAEs between left and right ears for the genders separately, and between genders for right and left ears separately. We found no significant differences.

Figure 3A shows a scatterplot of the SOAE level against the frequency. The plus signs represent SOAEs that are the strongest one for each ear (137). The dots represent all other SOAEs (614). With solid lines the 10 and 90 percentile levels of the noise floor are indicated in this figure. Figure 3B shows a line diagram of the relative distribution of SOAE-frequencies over 1/3-octave wide frequency classes. The levels of all SOAEs vary between -2 and 42 dBSPL (figure 3C). The levels of the strongest SOAE per ear vary between 1 and 42 dBSPL (mean 15 dBSPL). The level of the strongest SOAE in a right ear (16.0 dBSPL)

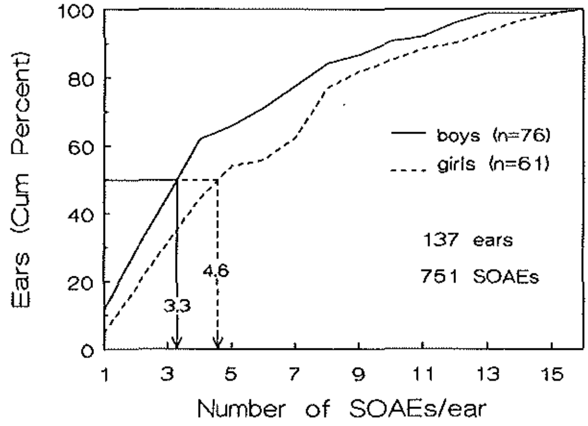


Figure 2
Cumulative distribution of the number of SOAEs per ear for boys and girls separately. The median number per gender is indicated.

is significantly stronger than in a left ear (13.5 dBSPL) (M-W, p=0.05). This level is not different between genders. Testing for differences in strongest levels between ears per gender, we found a higher level in right than in left ears of boys only (M-W, p=0.02). Table 2 shows the mean strongest SOAE level in ears, as well as the mean level of all SOAEs in these ears. We found no significant differences across ears and/or genders in mean SOAE level.

Table 2: Mean values of SOAE level characteristics.

	SOAE characteristics per ear (Mean values)		
Ears (n)	Total (137)	Boys (76)	Girls (61)
Strongest SOAE level (dBSPL)	14.8	13.9	16.0
Mean SOAE level (dBSPL)	8.0	7.6	8.5

DISCUSSION

The prevalence of SOAEs was 77.8% in 176 ears of 93 healthy newborns, ranging from 31 to 238 hours of age. This is higher than found by Burns et al *(1992)*, and Bonfils et al *(1989)*, who reported SOAE prevalences of 64% in ears of neonates, and of 68% in ears of infants younger than 18 months of age, respectively. Comparing these values with the previously reported SOAE prevalence of about 30% in adults *(Zurek, 1981; Fritze, 1983; Schloth, 1983; Wier, 1984; Kemp et al, 1986; Cianfrone, 1986; Probst et al, 1987; Rebillard et al, 1987)*, we conclude that the SOAE prevalence in healthy newborns is higher than in adults. Strickland and Burns *(1985)* reported a SOAE prevalence of 26 to 31% in children between 6 and 12 years. Given Bonfils' et al, Strickland and Burns' and our results, one might conclude that the SOAE prevalence significantly decreases between birth and about 6 years of age. However, this conclusion has no firm base, because the noise floors of the SOAE recording

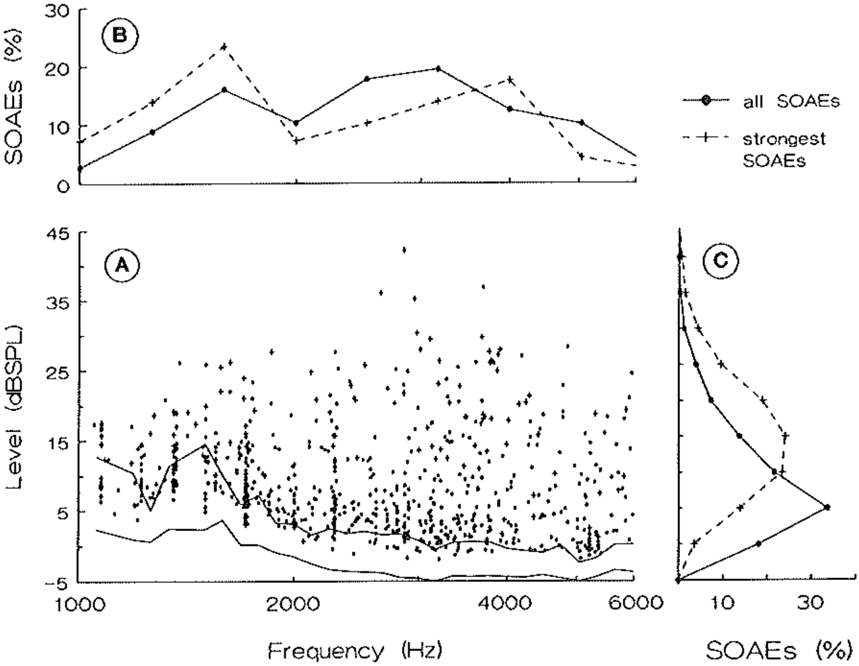


Figure 3
Panel A gives a plot of the SOAE levels against the frequencies. The strongest SOAE per ear is represented by a plus sign. The dots represent all other SOAEs. The 10, and 90 percentile levels of the noise floor of each SOAE are shown by solid lines. Panel B shows a line diagram of the SOAE frequency prevalence per 1/3 octave, and panel C of the SOAE levels.

are not readily comparable between studies, and probably differing.

It is obvious that prevalence rates of SOAEs are influenced by the noise floor of the SOAE recording and by the SOAE identification method. Although the noise floor cannot always be obtained from literature, we think it is unlikely that differing noise floors account for the SOAE prevalence difference between adults and healthy newborns we found. More important is recent evidence suggesting that the prevalence of SOAEs in human ears will increase as technological advances will permit SOAE recordings with reduced noise floors *(Martin et al, 1990; Probst et al, 1991; Long, 1991, personal communication)*. This questions the value of prevalence figures reported in different studies, with different noise floors. We propose that the SOAE prevalence should be determined and reported with reference to an absolute SOAE level criterion. The SOAE level dependent prevalence results of this study are shown in figure 4. In this figure our data are fitted by eye with a cumulative normal distribution function, which fits rather nicely. This is not surprising, since the number of SOAEs

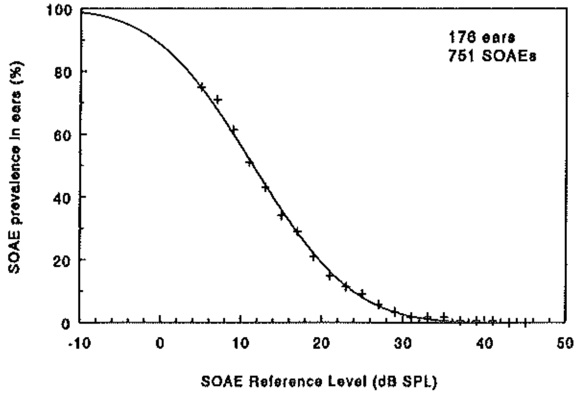


Figure 4
The SOAE prevalence is shown as a function of SOAE reference level. The solid curve fitted through the data is a cumulative normal distribution with a mean of 11.5 dB SPL and a variance of 95 (dB SPL)^2.

analyzed is high. When using a SOAE reference level of 20 dBSPL, the SOAE prevalence is about 20%. Because the noise floor of our data is rather high we were unable to reach a 100% prevalence. But, extrapolating our data, a 100% prevalence of SOAEs would have been found when using a SOAE reference level of -10 dBSPL in newborns.
In the study of Burns et al *(1992)* SOAE prevalence rates are compared between newborns and adults, while the noise floor of recording was different between both groups. They reported no significant prevalence difference. However, we think that a significant difference will appear if the prevalence is determined with reference to an absolute SOAE level.

In literature, the SOAE level in adults is reported to amount -10 to 20 dBSPL. We found the SOAE level in the newborn ears to range from -2 to 42 dBSPL. So, the levels of the strongest SOAEs in newborns in this study appear to be higher than in adults. Burns et al *(1992)* also found higher SOAE levels in neonates than in adults. Probably part of this SOAE level difference may be explained by the smaller ear canal volume in newborns *(Bray and Kemp, 1987)*. Of course, these level figures are influenced on the low level side by the noise floor of the SOAE assessment, and the SOAE detection criterion used. The number of low level SOAEs in our study is artificially low, because of the high noise floor of our SOAE recordings and the rather strict detection criterion applied: the minimally required signal to noise ratio is 4 dB.

In this study peaks at the frequencies 1147, 1428 and 1440 Hz were excluded. Looking at figure 3A there still appears to be clustering of SOAEs at some frequencies, for instance at 1355 and 1709 Hz, and the question arises whether this clustering is real or artifactual and due to external sound sources. As we could not identify these sources we tend to believe that the clustering is real.

In the ears of healthy newborns, SOAE frequencies above 2 kHz are the most prevalent. Also the frequency of the strongest SOAE in an ear is as often above 2 kHz. Strickland and Burns *(1985)* reported the highest SOAE prevalence in infants to be between 2 and 7 kHz, and between 2.5 and 5 kHz in neonates *(Burns et al, 1992)*. In adult ears the highest SOAE prevalence is reported to be between 1 and 2 kHz.

In short, with increasing age into adulthood, the overall prevalence of SOAEs is decreasing, as well as the level of the SOAEs. Also, the SOAE frequency distribution appears to change. A change in the middle ear acoustic transfer function has been proposed to be the reason for the frequency dependency of the SOAE prevalence. However, the development of the middle ear transfer has never been thoroughly studied. So, at this moment a developmental change of the inner ear may just as well be the cause of the SOAE differences with age.

In children above 6 years of age *(Strickland and Burns, 1985)*, and adults *(Rabinowitz and Widin, 1984; Cianfrone, 1986; Lonsbury-Martin et al, 1990b)* the mean number of SOAEs per ear varies between 1 and 4. In our newborn study, the number of SOAEs per ear ranges from 1 to 16, and has a mean value of 5.5. 54% of the 'SOAE' present ears shows 1 to 4 SOAEs per ear, 46% shows 5 to 16 SOAEs per ear. We think that the lower number of SOAEs per ear in children and adults compared with newborns is another feature of the developmental changes of the ear.

More than once study results in infants, children, and adults revealed that SOAEs do occur more frequently in females *(Zurek, 1981; Strickland and Burns, 1985; Lonsbury-Martin et al, 1990b; Burns et al, 1992)*. We found no SOAE prevalence difference between genders. However, the median number of SOAEs per ear is significantly lower in boys (3.3 vs. 4.6; figure 2). This was statistically significant. Given the abnormal distribution of the number of SOAEs per ear this was tested nonparametrically (M-W, p=0.04). The mean strongest SOAE level per ear does not differ between genders.

Another important issue is the fact that some studies found the prevalence of SOAEs to be higher in right than in left ears *(Bilger et al, 1990; Burns et al, 1992)*. We only found a tendency for a higher SOAE prevalence in right than in left ears. For the sexes separately we found a significant prevalence difference between right and left ears in girls. The number of SOAEs for right ears was significantly higher than for left ears, which was also reported by Burns et al *(1992)*. And the mean strongest level in right ears was significantly stronger than in left ears. For the sexes separately the difference between right and left ears appeared to be significant in boys only.

The bilateral SOAE prevalence rate is significantly higher than would be expected assuming ear independence (one-tailed p-value <0.0001, Binomial distribution with $p=0.778^2$). This was previously reported by Bilger et al *(1990)*, and Burns et al *(1992)*.

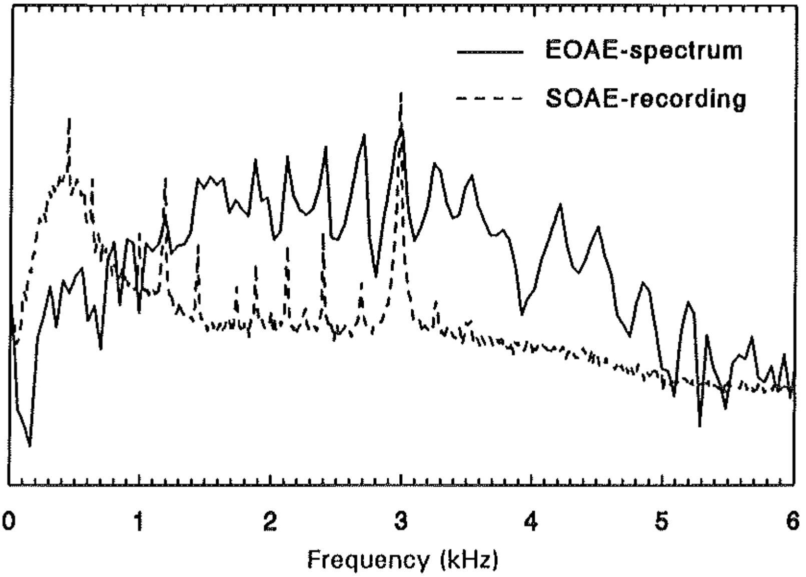


Figure 5
The spectrum of the EOAE recording is projected on the same axis as the SOAE spectrum recorded in that ear.

Comparing the spectra of the EOAE and SOAE recording, it struck us that often sharp peaks in the EOAE spectrum were seen when SOAEs were present. The SOAEs showed more or less the same frequencies as these EOAE spectrum peaks. We support the view that these peaks reflect SOAEs showing up in the EOAE too *(Wit et al, 1981)*. In figure 5, the EOAE and SOAE spectra of one ear are put into one figure. As can be seen, a strong correspondence exists between the frequency of a SOAE and a peak in the EOAE spectrum. However, a peak in the spectrum of the EOAE doesn't mean that a SOAE can be recorded at the frequency of this peak. A reason for this may be a problem with the signal-to-noise ratio of the SOAE registration. Or, in terms of oscillators *(VanDijk and Wit, 1988)*, SOAEs may be regarded as continuously active oscillators, which do show up in the EOAE recording, due to their synchronization to the click-stimulus *(Kemp, 1981; Ruggero et al, 1983; Norton and Neely, 1987)*. Peaks in the EOAE spectrum, at which frequencies we do not find SOAEs, may be regarded as damped oscillators, excited by the click during the EOAE recording, but inactive during SOAE recording. Reversely, we found two ears with a 'no EOAE' and a 'doubtful EOAE' visual score, which did show SOAEs. A tentative explanation is that in newborns a middle ear dysfunction in the first days post partum *(Chapter 2)* may prevent the SOAEs from being synchronized. Temporal averaging of an unsynchronized SOAE would appear as background noise of the EOAE recording.

As to the EOAE recordings, there appears to be a significant difference in response levels between adults and newborns *(Bray and Kemp, 1987)*. Bray and Kemp suggested that a reason for this may be the smaller ear canal volume in newborns. However, previously we hypothesized that the greater prevalence of SOAEs with high levels in newborns might also account for this EOAE response level difference between adults and newborns *(Chapter 3)*. To analyze the relation between SOAE presence and the strength of the EOAE in newborn ears, we compared the response level in all 176 ears, in 137 ears with a 'SOAE' present, and in 39 ears with 'no SOAE', or a 'doubtful SOAE'. In this analysis, the response of an EOAE recording was scored objectively as showing an EOAE present if the reproducibility amounted 40% or more. In all the ears tested the EOAE level ranged from 6.2 to 37.0 dBSPL (mean 21.2 dBSPL). In ears with a 'SOAE' present, the response level ranged from 7.2 to 37.0 dBSPL (mean 22.7 dBSPL), and in ears with 'no SOAE' or a 'doubtful SOAE' from 6.2 to 22.0 dBSPL (mean 16.0 dBSPL). The difference is significant (M-W, $p<0.001$). These findings support our hypothesis that 'SOAE'-presence in an ear might result in a stronger EOAE in this ear. Bonfils et al *(1990)* already reported a lower EOAE detection threshold in spontaneously emitting ears. We think that a strong EOAE amplitude and SOAE presence are related.

Recently Norton and Widen *(1991)* observed the greatest decrease in EOAE amplitude in children between 1 and 7 years. So in children older than 7 years of age one might expect the SOAE prevalence not to be different from adults. This is in accordance with Stricklands' findings in children from 6 to 12 years old and adults. Future studies on SOAE features may reveal developmental changes in the cochlea and/or middle ear between 0 and 6 years of age, and contribute to a better understanding of cochlear processes.

CONCLUSIONS

We conclude that the SOAE prevalence is higher in newborns than in adults. For instance SOAEs stronger than 20 dBSPL are rare in adults, while 20% of the SOAEs in newborns exceeds this level. The higher EOAE level in newborns compared with adults *(Chapter 3)*, is related to the higher prevalence of (stronger) SOAEs in newborns. The developmental changes in the level of SOAEs, and concomitantly in their prevalence, may occur in the first 6 years of life.

More research has to be done to determine to what extend developmental changes in properties of the ear canal and middle ear, as well as inner ear account for the SOAE frequency and level differences between newborns and adults.

APPENDIX

SOAE-LEVEL CALIBRATION

The sound pressure level per spectral bin and thus the strength of the SOAEs recorded by the ILO88 in mode 5 are displayed and stored to disk in log-units, but the reference sound pressure is not documented. Therefore we calibrated the strength in dBSPL by recording calibration spectra using the same recording method as used in the newborn, but with calibrated tonal sounds. A continuous tone produced by an audio stimulator (Medelec AS10) was transmitted into an anechoic test chamber (Brüel & Kjaer type 4222) and recorded with the ILO88 in mode 5. The level of the tone was measured by a calibrated instrument (Brüel & Kjaer type 2218 with a 4134 type microphone). The error in the calibration level is less than 1 dB in the frequency range 1 through 6 kHz. For a tone level of 20 dBSPL at tone frequencies 0.5 ,1.0, 1.5, 2, 3, 4, and 6 kHz calibration spectra were recorded. From these spectra a correction (in ILO88 units) for spectral differences in recording sensitivity was calculated for these seven frequencies. By linear interpolation corrections were calculated for all other frequency-bins of the spectra.

For stimulus levels in the range -5 to 55 dBSPL for the frequencies 1.5, 3, and 6 kHz calibration spectra were recorded. From these spectra the recorded level in ILO88 units was taken and linearly regressed against the calibration level. The slope-constant resulting from the regression analysis, which is the factor for conversion of ILO88 units to dBSPL, was 356.014 units/dB SPL.

Figure 6 shows the result of the spectral correction as well as the conversion to dBSPL for the calibration tones themselves. By definition these "input-output" curves intersect as 20 dBSPL (as this was our spectral calibration level). It is clear from figure 6 that at levels below 5 dBSPL the recorded level is incorrect, which is due to the background noise in the recording equipment. In the 5 to 50 dBSPL range the mean squared recording error is less than 1 dB. We concluded that in this range the SOAE levels reported in this study are accurate within 1.5 dB.

PEAK-IDENTIFICATION PROGRAM

A Turbo-Pascal program was written by the second author for automatic identification of spectral peaks in the recorded SOAE-spectra. The ILO88-recording in fact consists of two subaverages (labeled 'A' and 'B' in the ILO88), which are alternatingly acquired during one recording. The recorded averaged power spectra span the 0 to 6.25 kHz range with 512 equidistant frequency bins. The peak-identification program processed each recording as follows.

The grand average was calculated from the two subaverages, resulting in a spectral array consisting of 512 numbers each giving in logunits the strength of the sound in a specific frequency bin. Correction for spectral differences in recording sensitivity and conversion to dBSPL was done. In order to avoid identification of a large amount of spurious spectral peaks mainly in the noise background, spectral smoothing was done by convolution with an 13-point window (weights 0.2256, 0,1934, 0.1208, 0.0537, 0.0161, 0.0029, and 0.0002),

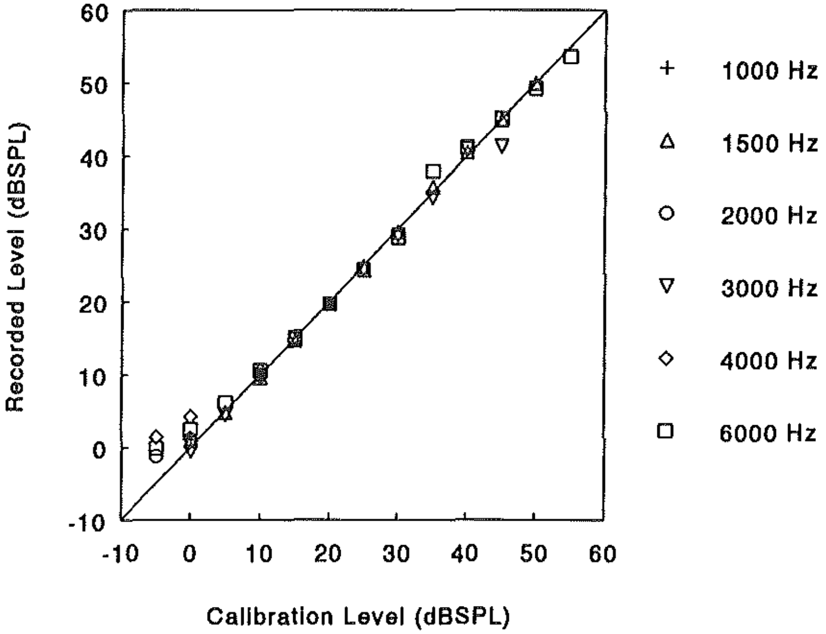


Figure 6

Recorded sound pressure levels, after correction for spectral sensitivity differences and calibration, as a function of the sound pressure level of calibration tones of various frequencies.

which was actually done by 6 times smoothing with a 3-point Hanning1 window (weights 0.25; 0.50; 0.25). For later identification of the constant spectrum level regions of the noise-floor below and above a spectral peak, the first derivative of the smoothed spectrum was calculated by subtraction of consecutive points. For later identification of spectral peaks, the second derivative of the smoothed spectrum was calculated. All frequency regions containing a spectral peak were identified by the negative extrema in the second derivative spectrum. Neighboring each peak two frequency regions, containing a spectral trough or constant spectrum level, were identified by the minimal values in the absolute first derivative of the smoothed spectrum. These two spectral troughs were considered as representative for the level of the noise floor. In the identified frequency regions, for each spectral peak and it's neighboring troughs the frequencies and levels were extracted from the original unsmoothed grand-averaged spectrum. As the two level values of the troughs were generally unequal, the level of the noise floor at the frequency of the peak was calculated by linear interpolation. For each spectral peak the signal-to-noise ratio was calculated by subtracting the noise-floor level from the peak level. Only spectral peaks with a signal-to-noise ratio exceeding 1.4 dB were kept for later statistical processing.

CHAPTER 6

CLICK-EVOKED OTO-ACOUSTIC EMISSIONS IN VERY-LOW-BIRTH-WEIGHT INFANTS: A CROSS-SECTIONAL DATA ANALYSIS

ABSTRACT

For the purposes of studying the phenomenon of Evoked Oto-Acoustic Emissions (EOAEs) in very-low-birth-weight (VLBW) infants, and the conditions affecting the utility of EOAE ear screening in this population, click-EOAEs were repeatedly recorded in ears of 144 VLBW infants, at different postconceptional ages of the infants, and at two different test sites, i.e. in the Neonatal High Care Unit (NHCU, ward), or at the neonatal outpatient clinic. The postconceptional age of the infants examined in the ward was 30 to 49 weeks and 37 to 66 weeks for the infants examined at the outpatient clinic. Overall 840 recording attempts were done. In the ward 86% of these attempts (388) were successful against 60% (of 452 attempts) at the outpatient clinic. In the latter group of infants the success rate of recording was only 33% at the corrected age of 6 months, which is significantly less than the 66% until the corrected age of 3 months. For a cross-sectional analysis of age effects one ear of each successfully recorded infant was selected.

Analysis of the 127 successful recordings revealed that the EOAE prevalence was 71% in the ward (54% for infants receiving extra oxygen per naso) and 91% at the outpatient clinic.

Compared with healthy newborns *(Chapter 3)*, VLBW infants are much more difficult to test especially at the outpatient clinic. However the EOAE prevalence at this test site is the highest and approaches that in healthy newborns. At the outpatient clinic response levels of EOAEs recorded approach levels found in healthy newborns. The higher success rate of recording in the ward and the lower EOAE prevalence are two counteracting factors as to the utility of EOAE based ear screening of VLBW infants.

INTRODUCTION

According to the high risk register for hearing disability *(Joint Committee on Infant Hearing, 1983)* one of the major risk factors for hearing impairment in infants is a birth weight less than 1500 g. The prevalence of hearing loss in these very-low-birth-weight (VLBW) infants is high. In the literature a prevalence of bilateral moderate to severe hearing loss of 2 to 4% is reported *(Durieux-Smith and Picton (Eds.), 1985; VanZanten et al, 1988)*. The overall prevalence of hearing impairment from mild to severe, uni-/bilateral in this high risk infant population is 10 to 100 times higher than in the infants not at risk *(Despland and Galambos, 1980; Lary et al, 1985; VanZanten et al, 1988)*. The prevalence of any form of hearing loss is only 0.37% in a population of pre-school Scandinavian children *(Kankkunen, 1982)*.

For early diagnosis of auditory dysfunction, infants at risk can be examined by Brainstem Electric Response Audiometry (BERA), a rather expensive and time-consuming method. There is no practicable test for mass screening on hearing impairment in neonates, yet.

However, the BERA thresholds appear to correlate rather well with presence or absence of Evoked Oto-Acoustic Emissions (EOAEs) in newborns *(Bonfils et al, 1988a,b; Stevens et al, 1990)*. In healthy newborns it becomes more and more accepted to screen for ear dysfunction with EOAEs. In this infant group an EOAE prevalence of 96 to 100% is reported *(Johnsen et al, 1983, 1988; Elberling et al, 1985; Stevens et al, 1987; Bonfils et al, 1988a,b, 1990; Chapter 3)*. In high risk babies in intensive care, this value is reported to amount to 79 to 93% *(Stevens et al, 1987, 1989; Bonfils et al, 1992)*.

This study involved EOAE recordings in VLBW infants made with commercial equipment, of which up till now only one brand is widely available (Otodynamics, London, UK). The infants were examined during their stay in the ward and at their follow-up visit to the outpatient clinic, so repeated tests were done at different postconceptional ages of the infants. The structure of data allows individual longitudinal as well as group cross-sectional data analysis; the latter is the type of this paper. An attempt for longitudinal data analysis will be done in a future paper. The aims of this study are:

1- To study the conditions in VLBW infants influencing the feasibility of the EOAE in ear function screening.
2- To determine the prevalence of EOAEs in VLBW infants.
3- To describe some basic features of the EOAE in VLBW infants in relation to features found in healthy newborns using the same equipment and procedures.

MATERIAL AND METHODS

SUBJECTS

EOAEs were recorded in ears of VLBW infants. The ***inclusion*** criteria were:

1) a birth weight of 1500 g or less,
2) a gestational age under 37 weeks,
3) the judgement 'stable enough for EOAE recording' by the paediatrician for infants examined in the ward.
4) parental informed consent

The ***exclusion*** criteria were:

1) head/neck malformations,
2) a family history/syndrome known for hearing impairment,
3) actual nasotracheal intubation for ventilation assistance for infants examined in the ward. After extubation the infant could still be included.

63 infants were included in the neonatal high-care unit (NHCU) of our hospital, which is a tertiary referral centre for a population of about 2 million. Infants were included in this

study from July 1991 to May 1992. After discharge they were followed up to a corrected age of 3 to 6 months.

In the same period 81 other infants were included after discharge from NHCU at their follow-up visit to our outpatient clinic. They were included and followed up to a corrected age of 3 to 6 months.

The 144 infants included ranged in gestational age from 25.3 to 36.0 weeks (mean 29.7 weeks), while their birth weights were between 610 and 1590 gram (mean 1150 g).

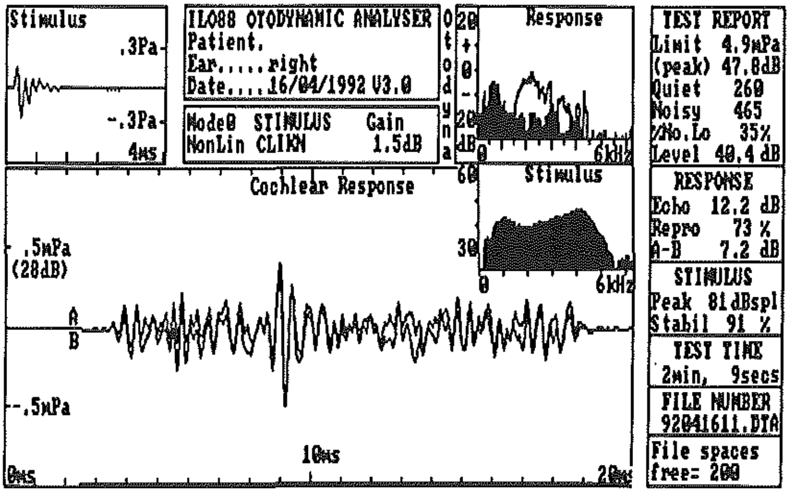
The state of oxygenation of the infants who are intubated for ventilation is followed by use of the intra-arterial oxygen pressure through a peripheral arterial line in the arteria tibialis/radialis, or a central umbilical line. The pressure is kept above 7.5 kPa. If infants get extra oxygen per naso or in the incubator they are monitored with a percutaneous oxygen saturation meter continuously, and the saturation is kept 92 to 97%. Infants without any extra oxygen are only monitored on indication.

To compare the basic features of EOAEs between VLBW infants and healthy newborns, we used the data of our EOAE study in 1036 ears of healthy newborns *(Chapter 3)*.

EQUIPMENT

In this study we used the ILO88 (Otodynamics, London, UK; software Version 3.0) for EOAE assessment. This equipment is described in detail elsewhere *(Kemp et al, 1990; Chapter 3)*. Therefore description here will be restricted. The stimulus used is a click, with a 80 μs electrical duration. Before starting the measurement, the operator can check the probe fit and the acoustical stimulus waveform. The stimulus waveform should be as click-like as possible, that is the initial pressure wave being as large as possible relative to subsequent pressure waves, and the spectrum should be as flat as possible. Response averaging is started when there is minimal noise leakage into the meatus. During the measurement an artefact-rejection criterion level ('Peak Limit', figure 1) can be adjusted manually.

The final result consists of two waveforms ('A' and 'B', figure 1). The root mean square response level ('Echo') is calculated from the grand average and the root mean square background noise level ('A-B') from the difference between the two subaverages. As a measure of their reproducibility, the correlation coefficient between the two subaverage waveforms ('Repro') is calculated too. The spectra of the response as well as the background noise are displayed. The stability of the probe fitting in the meatus ('Stabil') during the measurement is calculated. The final number of accepted sweeps ('Quiet'), and the actual measurement duration are recorded as well ('Test time').



ILO88 OTODYNAMIC ANALYSER
Patient.
Ear.....right
Date....16/04/1992 V3.0

Mode0 STIMULUS Gain
NonLin CLIKN 1.5dB

TEST REPORT
Limit 4.9mPa
(peak) 47.0dB
Quiet 260
Noisy 465
%No.Lo 35%
Level 40.4 dB

RESPONSE
Echo 12.2 dB
Repro 73 %
A-B 7.2 dB

STIMULUS
Peak 81dBspl
Stabil 91 %

TEST TIME
2min, 9secs

FILE NUMBER
92041611.DTA

File spaces
free= 200

Figure 1

The result of an EOAE recording in the ear of a VLBW infant, 30 weeks postconceptional age, showing a visually judged clear EOAE. It is a low-level EOAE showing no spectral energy below about 1.5 kHz, which cannot be explained by the rather flat stimulus spectrum. This female infant was born after a gestational age of 27 weeks and had a birth weight of 1175 g. The examination was done at the ward, while she had a naso-oesophageal tube and received extra oxygen in the incubator.

During the study, first the old version of the newborn probe with the solid epoxy tip was used. Rubber or silicon tubing around the tip was used to obtain acoustic sealing. Because this probe appeared to be too big for some of the newborn ears, we used for those ears a self-designed probe with a smaller tip size, but the same transducers. Later on we were able to use second-version newborn probes with disposable tips in 2 sizes, which can be used in the smaller ears. Sometimes one of the probes needed a couple of layers of leucopore tape wrapped around the tip to obtain an acceptable seal. In the two ears of one older infant (postconceptional age above 53 weeks) the adult probe was used, sealed into the ear canal with leucopore around the tip.

PROCEDURES

All EOAE recordings were done by the first author. Infants staying in hospital were examined weekly in the ward, lying in their incubator or crib. Hospital staff and parents were often present. At the neonatal outpatient clinic recordings were made when the infants had their follow-up visits. The infants were lying on their parent's lap or in a baby-car/-chair, during the examination. Most of the infants appeared to be asleep, some were awake and calm or slightly restless. None of the examination rooms was sound treated.

For each examination it was recorded whether it was made in the ward or at the outpatient clinic. A recording was considered successful either if 260 sweeps had been accepted or if the condition of the patient did not allow further testing and, visually judged, a clear EOAE was present or clearly no EOAE was present (and not to be expected if 260 sweeps would have been accepted). Also, the stimulus level of recordings showing no EOAE had to be above 72.5 dBSPL, otherwise the recording was scored as unsuccessful or was restarted, because the stimulus level had not been satisfactory.

For recording attempts in the neonatal ward simply the number of unsuccessful recording attempts was counted. For recording attempts at the outpatient clinic unsuccessful recordings were also identified on patient.

For each infant included, the perinatal characteristics, i.e. the birth weight, gestational age, Apgar score after 1 and 5 min., the umbilical pH, the use of ototoxic antibiotics and the maximal serum bilirubin were noted. These variables represent the patient history prior to that examination.

At the time of the examination, the (postconceptional) age and weight of the infants was registered, and whether the infants were naso-oesophageally intubated for food administration and/or received extra oxygen (per naso or in the incubator). These variables represent patient conditions at the time of the examination.

All recordings were stored on disk. Of each recording we stored data in a database on the probe type used, the stimulus level ('Peak'), the stability of the stimulus ('Stabil'), the artefact-rejection level ('Limit(peak)'), the measurement duration ('Test time') and the number of responses acquired in quiet ('Quiet'). The response variables stored on disk are mentioned below (see 'Data processing').

No otoscopy, or impedance testing was done in the infants, nor were they systematically screened by BERA.

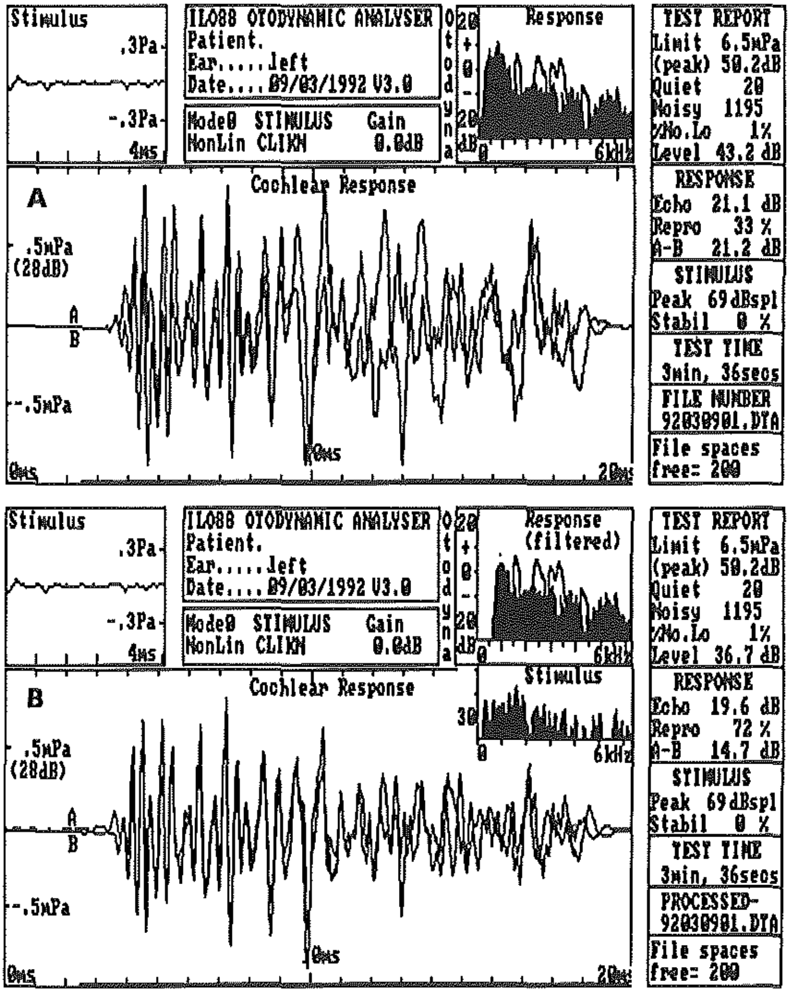
DATA PROCESSING

Age classification

The outpatient group was divided on the basis of the infants' postconceptional age at the time of testing in age classes of 43, 53, or 66 weeks (corresponding to the corrected ages of 3 weeks, 3 months and 6 months respectively).

Subjective EOAE score

The presence or absence of an EOAE was scored visually. Each response was subjectively scored as showing an 'EOAE', 'a doubtful EOAE', or 'no EOAE'. This manner of scoring was discussed in detail previously *(Chapter 3)*. Important factors in this manner of



ILO88 OTODYNAMIC ANALYSER
Patient.
Ear.....left
Date....09/03/1992 V3.0
Mode0 STIMULUS Gain
NonLin CLIKN 0.0dB

TEST REPORT
Limit 6.5mPa
(peak) 50.2dB
Quiet 20
Noisy 1195
%No.Lo 1%
Level 43.2 dB
RESPONSE
Echo 21.1 dB
Repro 33 %
A-B 21.2 dB
STIMULUS
Peak 69dBspl
Stabil 0 %
TEST TIME
3min, 36secs
FILE NUMBER
92030901.DTA
File spaces
free= 200

ILO88 OTODYNAMIC ANALYSER
Patient.
Ear.....left
Date....09/03/1992 V3.0
Mode0 STIMULUS Gain
NonLin CLIKN 0.0dB

TEST REPORT
Limit 6.5mPa
(peak) 50.2dB
Quiet 20
Noisy 1195
%No.Lo 1%
Level 36.7 dB
RESPONSE
Echo 19.6 dB
Repro 72 %
A-B 14.7 dB
STIMULUS
Peak 69dBspl
Stabil 0 %
TEST TIME
3min, 36secs
PROCESSED-
92030901.DTA
File spaces
free= 200

Figure 2

The result of an EOAE recording in the ear of a VLBW infant of about 3 months corrected age, showing a visually judged EOAE present. This is a high noise EOAE recording done at the outpatient clinic with only 20 sweeps accepted. The displayed stimulus (spectrum) seems inadequate, but this is probably just caused by 'accidental' ending of the recording, since an EOAE is present. Figure 2A shows the unfiltered, 2B the filtered response. As can be seen, the reproducibility increases from 33 to 72% by filtering. A comparable method of signal processing is done in the fast screening protocol of the recent version of the ILO88. This male subject was born after 29 weeks gestational age and had a birth weight of 1170 g.

scoring are the response waveform, its reproducibility and the relative strength of the frequencies in the spectrum of the response, arising above the background noise. Our scoring method is tolerant of responses in which only part of the waveform is reproduced.

Objective EOAE variables

Of each response, its level, absolute reproducibility, and background noise were obtained. These same variables were obtained after filtering the response above 1 kHz, with the help of the ILO88 program itself (figure 2).

Success rate of recording

The success rate is defined as the percentage of all recording attempts that were successfully completed. As clarified below in the discussion, this methodological error only slightly corrupted the success rate figures. Only a successful recording can show absence or presence of an EOAE. So, the prevalence of EOAEs is independent of the success rate. The success rate was calculated separately for recordings in the ward and at the outpatient clinic. To enable analysis of possible differences between those infants at the outpatient clinic in which the recording attempts were unsuccessful and the others, patients needed to be assigned to either one of these groups to avoid comparison of the same patient data emerging in both groups. We were unable to perform this analysis for the inpatients, because patient data were not registered for unsuccessful recordings.

Data selection for cross-sectional analysis of successful recordings

Because of the cross-sectional character of this paper and the dependence of both ears in the same infant, one ear of each infant was selected only once for further processing in order to enable studying the EOAE data as a function of age. This was accomplished by assigning a random number to each recording in the set of recordings for a specific infant. Per infant the recording with the lowest random number was selected. In this way, 49 infants were selected at the ward, 78 at the outpatient clinic.

Table 1: Success rates of all recordings made in the ward or at the outpatient clinic for infants of several postconceptional age (PCA) classes.

		n recording attempts	success rate
all infants		840	72% (605)
inpatients (mean PCA 34.5 weeks)		388	86% (334)
outpatients	all	452	60% (271)
PCA classes	43	213	64% (137)
(weeks)	53	157	68% (107)
	66	82	33% (27)

Figures in parentheses indicate numbers of recordings.

RESULTS

Table 1 shows the success rates for EOAE recordings in ears of infants of different age classes and at the two different test sites. Overall, 840 recording attempts were done in 144 infants. 605 successful recordings were made in 127 infants either in the ward or at the outpatient clinic. 117 infants were successfully examined bilaterally at least once, and 10 unilaterally only. So, 244 different ears were tested. 133 of these ears were from boys and 111 from girls. Summarising, 605 successful recordings were made in 244 ears of 127 infants. This means that on average each ear was examined 2.5 times (605/244) at times rather uniformly distributed over the postconceptional age range from 29.1 to 66.1 weeks.

Of the 840 recording trials 388 were done in the ward, of which 334 (86%) were successful in 63 infants.

At the outpatient clinic 271 (60%) of 452 recording trials were successful. When the infants are about 66 weeks postconceptional age, the success rate halves compared to the other age classes (33% vs. 64-68%) tested at the outpatient clinic.

The remaining part of the results section describes results after cross-sectional data selection.

Table 2: Perinatal characteristics of all 127 infants successfully tested, and separately for those tested in the ward or at the outpatient clinic.

	all infants n=127	inpatients n=49	outpatients n=78	difference
Birth weight (g)	610 - 1590 (1150)	610 - 1530 (1085)	670 - 1590 (1190)	$p<0.05$
Gestational age (weeks)	25.3 - 36.0 (29.7)	25.4 - 35.4 (29.4)	25.3 - 36.0 (29.9)	n.s.
Apgar 1 min	0 - 10 (5.8)	0 - 9 (5.9)	1 - 10 (5.8)	n.s.
Apgar 5 min	5 - 10 (8.2)	5 - 10 (8.3)	5 - 10 (8.1)	n.s.
Umbilical pH	6.70 - 7.40 (7.21)	6.70 - 7.40 (7.21)	6.84 - 7.39 (7.22)	n.s.
Use of ototoxic antibiotics (days)	0 - 17 (1.4)	0 - 11 (1.3)	0 - 17 (1.4)	n.s.
Maximal serum bilirubin (μmol/l)	60 - 256 (142)	78 - 256 (143)	60 - 222 (142)	n.s.

Difference was determined by the T-test; n.s. = not significant.
Figures in parentheses indicate mean values.

Table 2 shows the perinatal characteristics of all 127 infants successfully recorded in this study, and separately for those selected in the ward and those selected at the outpatient clinic. Only the birth weight of infants tested in the ward is significantly lower than of infants tested at the outpatient clinic.

Table 3 shows some data describing the patient condition at the time of the recording. It shows the weight and (postconceptional) age, whether the infant was naso-oesophageally intubated for feeding, and if it received extra oxygen per naso or in the incubator. Also it was registered whether the infant was examined in an incubator/bed or in a chair/on a parents lap, and which probe was used. Obviously, the weight and (postconceptional) age of the infants tested in the ward is lower than of those tested at the outpatient clinic. 82% of the inpatients was naso-oesophageally intubated for food administration. The oxygen use per naso in the ward was about 5 times higher than at the outpatient clinic. As much as 82% of the recordings in the ward was done while the infants were lying in an incubator. The frequency of use of the three different probe types is only slightly different between the groups.

Table 3: Patient condition at the time of EOAE recording, for recordings in the ward and at the outpatient clinic separately.

		recordings in the ward (n=49)	recordings at outpatient clinic (n=78)
Weight (g)		755 - 2585 (1540)	2780 -7600 (4620)
Postconceptional age (weeks)		30.0 - 48.7 (34.4)	39.6 - 67.4 (50.2)
Age (weeks)		0.7 - 14.4 (5.0)	12.1 - 40.0 (20.3)
naso-oesophageal intubation for feeding		82%	0%
oxygen	per naso	27%	5%
	in incubator	12%	0%
Incubator/bed		82% / 18%	0%
chair/lap		0%	100%
Probe	solid tip	22%	26%
	our design	14%	8%
	disposable tip	63%	66%

Figures in parentheses indicate mean values.

Table 4: Recording parameters influencing the feasibility of EOAE screening in VLBW infants.

	all recordings (127)	recordings in the ward (49)	recordings at outpatients clinic (78)	difference*
Stimulus level (dBSPL)	63 - 96** (78)	69 - 96** (79)	63 - 96** (77)	p<0.05
Artefact rejection level (dBSPL)	44.6 - 52.0 (49.3)	44.6 - 51.3 (48.4)	46.0 - 52.0 (49.8)	p<0.001
Stimulus stability (%)	0 - 100 (72)	10 - 100 (80)	0 - 100 (68)	p<0.005
Number of sweeps accepted	7 - 260 (153)	29 - 260 (214)	7 - 260 (115)	p<0.001
Test time (s)	60 - 950 (269)	60 - 950 (293)	70 - 760 (254)	n.s.

* T-test; ** upper limit of ILO88's measurement range. Figures in parentheses indicate mean values.

FEASIBILITY

Table 4 shows statistics on the recording parameters that may influence the feasibility of EOAE screening in VLBW infants. The recording parameters are shown for all ears, ears tested in the ward or at the outpatient clinic, separately. As can be seen, the artefact rejection level of the recordings done in the ward is significantly lower than for those done at the outpatient clinic. The stimulus level and stability are significantly higher in the ward. The test duration is the same at the two test sites, but the number of accepted sweeps is significantly higher in the ward.

PREVALENCE

The prevalence of EOAEs in ears of VLBW infants is shown in table 5 for recordings done in the ward and at the outpatient clinic at different ages. The bottom row shows results in 218 ears of healthy newborns older than 4 days extracted from a previous study *(Chapter 3)* of 1036 ears. The number of ears with and without an EOAE as well as the percentages are shown. There were 2 ears (4%) of inpatients, 1 (1%) ear of outpatients, and 2 ears (1%) of healthy newborns showing a 'doubtful EOAE', and these were counted as 'no EOAE' ears in table 5. As can be seen, 71% of the ears tested in the ward shows an EOAE, while the mean EOAE prevalence at the outpatient clinic amounts to 91%.

Table 5: Prevalence of EOAEs in ears of VLBW infants examined in the ward or at different ages at the outpatient clinic.

	n recordings	EOAE (n recordings)	no EOAE or doubtful (n recordings)
VLBW infants			
all recordings	127	83% (106)	17% (21)
inpatients (mean PCA 34.4 weeks)	49	71% (35)	29% (14)
extra O_2 per naso	13	54% (7)	46% (6)
outpatients all	78	91% (71)	9% (7)
PCA classes 43	42	91% (38)	9% (4)
(weeks) 53	28	93% (26)	7% (2)
66	8	88% (7)	12% (1)
Healthy newborns			
age > 4 days	218	97% (211)	3% (7)

PCA = postconceptional age. Figures in parentheses indicate numbers of recordings.

BASIC EOAE FEATURES

Restricting analysis to the ears with EOAEs present according to our visual score, table 6 shows the response variables (also filtered above 1 kHz). The response level is significantly higher in the recordings made at the outpatient clinic. These recordings are stronger but have a significantly higher background noise level too. The response reproducibility in the two groups is comparable.

Again for comparison, basic features of 211 EOAEs in 218 ears of healthy newborns older than 4 days are shown in table 6 also. As can be seen, EOAEs are stronger in healthy newborns than in VLBW infants, although the (older) VLBW infants examined at the outpatient clinic have response levels approaching those of the healthy newborns. The reproducibility of the EOAE in healthy newborns is higher than in VLBW infants. The background noise level in healthy newborns is significantly less compared to VLBW infants examined in the outpatient clinic but about equal to that in the VLBW infants examined in the ward.

DISCUSSION

The success rate of EOAE recordings in VLBW infants (table 1) in the ward (86%) is higher than at the outpatient clinic (60%). Infants tested at the outpatient clinic until the corrected age of 3 months are tested with a rather constant but low success rate (64-68%). For the older infants the success rate is half of that of the younger age groups tested at the outpatient clinic. This can be explained by the fact that the older infants are more often awake and restless. Also, the older infants have significant cerumen produc-

Table 6: Basic features of the EOAEs in ears of VLBW infants (in the ward or at the outpatient clinic) and in ears of healthy newborns.

	VLBW infants				Healthy newborns		
	all recordings (106)	recordings in the ward (35)	recordings at outpatients clinic (71)	difference	all recordings (211)	difference to VLWB inpatients	difference to VLWB outpatients
Response level (dBSPL)	5.4 - 33.0 (18.4)	5.4 - 26.5 (15.2)	9.7 - 33.0 (20.0)	p<0.001	6.2-37.8 (21.9)	p<0.001	p<0.05
Response reproducibility (%)	0 - 99 (67)	20 - 98 (71)	0 - 99 (66)	n.s.	34-99 (90)	p<0.001	p<0.001
Background noise level (dBSPL)	1.6 - 24.3 (12.5)	1.6 - 17.8 (8.8)	4.1 - 24.3 (14.4)	p<0.001	1.8-18.2 (7.7)	n.s.	p<0.001
	Filtered above 1 kHz						
Response level (dBSPL)	2.2 - 32.9 (17.5)	2.2 - 26.2 (14.6)	6.9 - 32.9 (19.0)	p<0.001			
Response reproducibility (%)	3 - 99 (79)	36 - 98 (80)	3 - 99 (79)	n.s.			
Background noise level (dBSPL)	-0.5 - 19.1 (8.3)	-0.5 - 15.3 (5.4)	0.3 - 19.1 (9.8)	p<0.001			

Difference was determined by the T-test; n.s. = not significant. Figures in parentheses indicate mean values.

tion, which necessitated frequent cleaning of the probe and repositioning before starting the examination. Consequently, older infants were aroused more often. There appears to be no significant difference in birth weight or gestational age between successfully and unsuccessfully examined infants, meaning that not perinatal patient data, but patient condition prior to or at the time of the recording determines the success. We could test this for the outpatient group only, but we cannot think of any reason why this should not apply to the inpatient group too. In summary, the success rate of EOAE recordings in VLBW infants appears to be dependent on test site as well as on age. The success rate is higher in the ward than at the outpatient clinic, and at the outpatient clinic higher for the infants younger than about 3 months corrected age. There appears to be no relation between perinatal patient data and the success rate at the outpatient clinic.

The success rate percentages may be biased by the fact that their calculation is based partly on the same ears. We were forced to perform the success rate calculation this way, because the unsuccessful recording attempts in the ward were not identified on infants. On average each ear was tested only 2.5 times, so the success rate is probably only slightly influenced. This will be discussed below.

The success rate of EOAE recordings in ears of VLBW infants is much poorer than in 1036 ears of healthy newborns examined in the ward, in whom we reached a success rate of 96% *(Chapter 3)*. This is probably caused by the differences in test environment and infant status, being less favourable for the often stressed VLBW infant examined at a noisy NHCU or temporarily out of their home environment at the outpatient clinic.

This study aims to describe factors affecting the feasibility of EOAE screen in VLBW infants, the basic features and the prevalence of the EOAEs in this group. The two ears of one infant are not independent, and therefore of each infant only one ear was included once by randomized selection.

The lower birth weight of infants examined in the ward is the only perinatal characteristic (table 2) significantly different between the infant groups tested at the two different test sites. This can be explained by the fact that infants with the higher birth weights are transferred back to other hospitals sooner. Because their stay in our hospital was short, these infants had less chance to be included in the study while staying in the ward. They had a higher chance on getting their first examination at their regular visits to the outpatient clinic.

Regarding the patient variables at the time of the recording (table 3), it is inherent to this study that when ears are examined in the ward the weight and the (gestational) age of the infants is lower than at the outpatient clinic.

The use of probe types is not very different between the in- and outpatient recordings. An earlier paper *(Chapter 3)* described the intertransducer sensitivity variation measured over 5 probes. Averaged over frequencies, the absolute measurement error of the ILO88 system was less than 3 dB for each probe. Therefore there appears to be no reason to think that the probes used in this study should influence the EOAE recording variables.

82% of the infants whose ears were tested in the ward were lying quietly in an incubator. This may be one of the reasons for a higher success rate of the EOAE recordings, since the incubator shuts off much of the environmental noise of a NHCU. Unfortunately, we cannot prove this, because for recordings done in the ward it was just counted if they were successful or not. So we cannot check whether the unsuccessful recording attempts were done while the infants were lying in an incubator or not. Still we think that the fact that most of the recordings done in the ward were made while the infant was lying in the relatively quiet incubator may cause the success rate difference in the ward and at the outpatient clinic.

We also think that naso-oesophageal intubation for feeding as well as obtaining oxygen per naso or in the incubator may influence the success rate unfavourably, probably both indirectly by middle ear irritation, and directly by enhanced levels of body sounds. These subjective remarks rise from gained experience with EOAE recording by the first author in examining VLBW infants.

FEASIBILITY

Table 4 showing the recording parameters influencing the feasibility of EOAE screening in VLBW infants suggests that the EOAE recording is easier in the ward. The stimulus level, the artefact rejection level, the stimulus stability and the sweeps accepted in a comparable test duration is more favourable for the inpatient recordings. This is in agreement with the difference in overall success rates between the two test sites.

PREVALENCE

The mean prevalence of EOAEs in ears of VLBW infants is 71% when tested in the ward and 91% when tested at the outpatient clinic. These prevalences are lower than in healthy newborns tested at least 4 days after birth. In an earlier paper *(Chapter 3)* we found the EOAE prevalence to be age dependent in healthy newborns. We reported then a rise in prevalence from 78% in ears of newborns younger than 36 hours to 99% in ears of newborns older than 108 hours. The lower EOAE prevalence reported now in ears of VLBW infants tested in the ward cannot be explained by this age relation shortly after birth, since all infants included in the present study were older than 108 hours when tested.

The EOAE prevalence in the ward is lower for infants receiving extra oxygen per naso. The prevalence amounts to 77% in ears from infants not receiving extra oxygen per naso compared to 54% in ears from infants who do. The latter group of infants generally had needed naso-tracheal intubation in order to be ventilated for a longer period of time. This factor as well as the oxygen per naso at the time of the recording can cause an abnormal middle ear transfer and therefore no detectable EOAE.

In the search for an optimal combination of test site and infant status for EOAE screening in VLBW infants, success rate and prevalence are counteracting factors. The ward is the most successful site, while EOAE prevalence is higher at the outpatient clinic. We propose to screen VLBW infants at the outpatient clinic, before the corrected age of 3 months. The EOAE prevalence in this age group seems high enough for screening purposes (91%). The mean success rate of EOAE recording in this age group is 65% after one attempt. In our study we calculated a success rate of 84% after two recording attempts in the same age group. Remarkably, in theory a 88% success rate can be reached after two recording attempts when using the mean success rate of 65% found in infants younger than 3 months corrected age. Apparently, the chance to make an unsuccessful recording is only slightly higher if a previous recording attempt was unsuccessful. Besides the proposal to screen VLBW infants at the outpatient clinic, before the corrected age of 3 months, we think in the ward infants receiving extra oxygen per naso for a longer period of time should better be examined later, because the success rate here is 86%, but the EOAE prevalence in this subgroup of VLBW infants is only 54%.

BASIC EOAE FEATURES

The basic features of EOAEs in VLBW infants were studied in the ears with EOAEs present. The response level appeared to be significantly higher in the recordings made at the outpatient clinic. In an earlier paper in healthy newborns *(Chapter 2)* we reported that the EOAE response level increased with age shortly after birth. We think this growth might be due to changes in the middle ear function, caused by clearance of the middle ear from (amniotic)fluid. The rate of EOAE growth is very different between individuals. It might even take longer in VLBW infants. Maturation of the inner ear might also explain the change with age of EOAE response level in VLBW infants. Given the results in the literature on the maturation of other aspects of the cochlea *(Anniko, 1985)* it is to be expected that maturation of the EOAE will be completed already at a gestational age of at most 3 months. This is in agreement with the fact that the response levels of ears tested at the outpatient clinic differing between 37.2 and 66.1 weeks postconceptional age approach the levels found in healthy newborns.

The mean response reproducibility of recordings done in the ward and at the outpatient clinic is comparable but significantly lower than in healthy newborns. The reproducibility of recordings in VLBW infants done at the outpatient clinic is as low as in those done in the ward, despite the higher response levels at the outpatient clinic. Referring to the relation between the response level and reproducibility *(Chapter 3)* it appears that the higher background noise level in VLBW infants tested at the outpatient clinic than in those tested in the ward can explain the relatively low reproducibility at the outpatient clinic. The background noise level of recordings in VLBW infants made in the ward is comparable with the background noise level in healthy newborns.

We also filtered the EOAE response above 1 kHz (figure 2 and table 6), because in a significant number of cases strong EOAE frequencies clearly arose in the spectrum of the response above the background noise, although no clear reproducibility of the two response waveform traces was seen. The background noise was predominantly located below 1 kHz. So, after filtering the response above 1 kHz, the visual reproducibility of the response waveform improved. Also, the reproducibility figures displayed by the ILO88 correspond much better with our objective 'Repro' criterion of 40-50% or more for ears with EOAEs present *(Chapter 3)*. A reproducibility of over 40% after filtering is found in 93% of the ears with a visually scored EOAE present, compared to 84% before. And only 2.6% of the ears that failed the subjective visual screen pass the objective

EOAE screen after filtering, compared to 1.7% before. So filtering above 1 kHz is a rather safe method to facilitate visual EOAE scoring and to obtain objective reproducibility figures fitting well with a 40-50% 'Repro' criterion for EOAE presence.

CONCLUSION

1- VLBW infants are more difficult to test than healthy newborns. This is even more so when the VLBW infants are above 3 months corrected age.
2- The most important factor negatively influencing the success rate of EOAE recording in VLBW infants is probably infant noise/stress.
3- The prevalence of EOAEs in ears of VLBW infants examined in the ward is low (71%) compared with VLBW infants tested at the outpatient clinic (91%) and healthy newborns (97%).
4- EOAE screening in VLBW infants should be done preferably either while the infants are still in the ward and are not receiving any extra oxygen per naso or at the outpatient clinic before the corrected age of 3 months.
5- The response levels of ears of VLBW infants tested at the outpatient clinic differing between 37.2 and 66.1 weeks postconceptional age approach the levels found in healthy newborns.

CHAPTER 7

LONGITUDINAL BEHAVIOUR OF THE CLICK-EVOKED OTO-ACOUSTIC EMISSION IN VERY-LOW-BIRTH-WEIGHT INFANTS

ABSTRACT

The Click-Evoked Oto-Acoustic Emission (EOAE) was studied in very-low-birth-weight (VLBW) infants, in search for a reflection of the developmental changes of the ear on the EOAE. Repeated recordings were made in ears of 144 VLBW infants at two different test sites, i.e. the neonatal high care unit and the outpatient clinic, and at different postconceptional ages of the infants, i.e. from as soon as they were stable enough for EOAE recording until 3 to 6 months corrected age. For a case wise longitudinal analysis a selection was made of infants in whom 4 or more successful bilateral EOAE recordings were done. Compared to the success rate of EOAE recording and the presence of EOAEs in our previous cross-sectional data analysis this selected subgroup appeared representative. The 22 selected infants ranged in gestational age from 25.3 to 32.0 weeks, while their birth weights were between 720 and 1410 g. Before about 40 weeks postconceptional age, the individual EOAE level, and therefore also the visual EOAE score (present/absent) is strongly variable. Patient condition variables like lying in an incubator, receiving extra oxygen per naso or naso-oesophageal intubation for food administration appear to have no direct influence on EOAE level or presence. We think the large variations are related to the high prevalence of (transient) middle ear effusion in VLBW infants. Per individual ear, the strongest EOAEs are recorded at a higher postconceptional age at the outpatient clinic. Consequently, EOAE presence is more stable then. The overall mean EOAE level increases with age until about 43 weeks post conception. In some ears mainly high frequency energy is found in the early, and gradually more low frequency energy in the later recorded EOAE spectra. These changes might in theory be a reflection of ear maturation. This longitudinal study of selected VLBW infants, resulted in an EOAE presence that increased to 95% after repeated recordings (42/44 ears; 21/22 infants).

INTRODUCTION

Infants with a very-low-birth-weight (VLBW), i.e. less than 1500 g, are at risk for hearing disability *(Joint Committee on Infant Hearing, 1991)*. The overall prevalence of hearing impairment from mild to severe, uni-/bilateral in this high risk infant population appears to be 10 to 100 times higher than in the infants not at risk *(Despland and Galambos, 1980; Lary et al, 1985; VanZanten et al, 1988)*. In both populations Brainstem Electric Response Audiometric (BERA) thresholds appear to be related to the presence or absence of Evoked OtoAcoustic Emissions (EOAEs) *(Bonfils et al, 1988a,b; Stevens et al, 1990; Kennedy et al, 1991; Webb and Stevens, 1991)*. Therefore EOAE ear function screening may be a good method for the early detection of auditory dysfunction too, while in healthy newborns this manner of ear function screening becomes more and more accepted.

Before EOAE recording may become a viable screening method in VLBW infants, it is important to study the feasibility of the EOAE recording, to describe the basic EOAE features and the EOAE prevalence in this population.

In VLBW infants, who are generally born prematurely, the aspect of maturation may be of influence on EOAE characteristics. EOAEs need to go retrograde through the middle ear after which they can be registered in the external ear canal. Developmental changes, which do occur in the outer, middle, and inner ear of VLBW infants may affect EOAEs.

In a previous paper *(Chapter 6)* we reported on a cross-sectional group wise data analysis of EOAEs in VLBW infants between 30 and 66 weeks postconceptional age. Part of the infants was tested in the Neonatal High Care Unit (NHCU), and the other part, at an older age, at their follow-up visits at the outpatient clinic. The success rate of making a recording was higher in the ward (86%) than at the outpatient clinic (60%). In contrast with the success rate, the EOAE prevalence in the successful recordings was lower in the ward (71%) than at the outpatient clinic (91%). The levels of recorded EOAEs were higher at the outpatient clinic. So, as the infants tested at the outpatient clinic were older than those tested in the ward, there might have been an increase with age in EOAE prevalence and level.

This longitudinal study describes the 'normal' behaviour of the EOAE recorded in preterm born infants in the period in which the inner ear is reported to fully mature *(Anniko, 1985)*. Obviously, truly normal behaviour cannot be recorded with present techniques in this postconceptional age range. All VLBW infants are by definition abnormal. Nevertheless, as it is probably the closest approximation to normal that is possible now, we decided to 'monitor' the development of the EOAE in this specific population. Repeated recordings were made in the same infant/ear at the two different test sites, and at different postconceptional ages of the infant. We mainly aimed at answering the question, whether there is a systematic change of the EOAE with age distinguishable in this population of VLBW infants, and whether the change is as expected on the basis of what is known about inner ear maturation.

Also the perinatal characteristics, the patient and test site conditions at the time of the recording, which may be influencing the EOAE recording were analyzed. All EOAE recordings were done with commercially available equipment.

MATERIAL AND METHODS

SUBJECTS

EOAE recordings were made in ears of VLBW infants. They were included from the NHCU and outpatient clinic, if their birth weight was less than 1500 g and their gestational age below 37 weeks. Per year about 150 VLBW infants with a birth weight less than 1500 g and a gestational age below 37 weeks are admitted to our hospital. One third of this population is born with a weight between 500 and 1000 gram. About 90% of the infants with a birth weight below 1000 g has to be ventilated with a mean duration of 18 days, against about 70% of the infants with a birth weight above 1000 g with a mean duration of 10 days. Bacterial meningitis occurs in less than one infant per year. About 25 infants a year (17%) have an intraventricular bleeding. Grade III and IV bleeding, according to Papile *(1978)*, which may have a negative effect on the infants' development, occurs only sporadically. About 3 infants a year (2%) get a hydrocephalus subsequent to an intraventricular bleeding. Icterus neonatorum is closely monitored in our hospital and if necessary treated by phototherapy.

The VLBW infants were only included in this study, if they were judged stable enough for EOAE recording by the paediatrician, and after parental informed consent. Infants were excluded if they showed head/neck malformations and/or had a family history/syndrome known for hearing impairment. Infants were also (temporarily) excluded if they were naso-tracheally intubated for ventilatory assistance. This last exclusion criterion was set after experiencing already great difficulties in recording EOAEs in unintubated VLBW infants.

In the period from May 1991 to November 1992, 144 infants were included. They were followed up to a corrected age of 3 to 6 months. These infants ranged in gestational age from 25.3 to 36.0 weeks (mean 29.7 weeks), while their birth weights were between 610 and 1590 gram (mean 1150 g). The mean Apgar score after 5 minutes varied from 5 to 10 (mean 8.2).

So, between May 1991 and November 1992 we included about 65% of the total population of VLBW infants admitted to our hospital. Causes for non inclusion, besides the exclusion criteria mentioned above, were death, early transfer to a secondary referral hospital, and scheduling difficulties.

Patient selection for case wise longitudinal analysis

For a case wise longitudinal analysis we selected 22 infants out of 144, in whom 4 or more successful bilateral examinations were done. Table 1 shows the birth weight and gestational age of these selected infants, as well as the weight and postconceptional age range at which successful recordings were done. The data of the unsuccessful recordings done in the same infants at the outpatient clinic were also analyzed. The gestational age of the selected 6 girls and 16 boys ranged from 25.3 to 32.0 weeks (mean 28.1 weeks), while their birth weights were between 720 and 1410 gram (mean 1040 g). The Apgar score after 5 minutes varied from 5 to 10 (mean 8.5). All 13 (100%) infants born with a weight of 1000 gram or less received ventilatory assistance from 1 to 56 days (mean

Table 1. Features of 22 selected VLBW infants, in whom 4 or more successful bilateral EOAE recordings were done. The infants are numbered, their sexe, gestational age (GA) and birth weight are given in the first 3 columns. The last 2 columns show the weight and postconceptional age (PCA) range at the time of successful recordings.

Infant nr/sexe	birth weight (g)	GA (weeks)	Weight range at time of successful recording (g)	PCA range at time of successful recording (weeks)
1 / ♂	1410	29.0	1380 - 7205	31.3 - 66.2
2 / ♀	860	26.3	1275 - 4210	31.0 - 45.8
3 / ♂	1360	31.6	1210 - 4840	32.3 - 53.1
4 / ♀	730	29.3	690 - 4300	31.0 - 52.6
5 / ♂	1345	31.9	1325 - 5500	32.3 - 52.6
6 / ♂	875	32.0	860 - 4790	32.9 - 55.8
7 / ♂	1400	28.3	1200 - 6640	29.4 - 56.8
8 / ♀	850	28.4	1030 - 6145	31.3 - 65.0
9 / ♂	1255	29.4	1210 - 5720	31.1 - 53.4
10 / ♀	875	26.1	1870 - 5885	34.1 - 55.5
11 / ♂	840	30.1	860 - 2935	31.4 - 44.9
12 / ♀	1150	30.0	1210 - 4365	31.7 - 55.7
13 / ♂	1240	28.1	1780 - 3700	35.2 - 46.6
14 / ♂	1050	26.9	2155 - 7975	35.7 - 68.1
15 / ♂	995	26.1	1225 - 3930	30.9 - 46.8
16 / ♀	1000	26.7	1630 - 3315	32.9 - 42.9
17 / ♂	720	25.6	1900 - 5035	36.1 - 53.0
18 / ♂	905	26.0	1810 - 3230	35.0 - 42.1
19 / ♂	835	26.1	1685 - 3050	34.2 - 43.8
20 / ♂	1305	28.0	2045 - 3785	34.9 - 51.2
21 / ♂	975	25.3	2180 - 5930	36.6 - 58.5
22 / ♂	875	26.4	1930 - 3860	35.1 - 51.0

19 days). Seven (77%) of the nine infants born with a weight between 1000 and 1500 gram had to be ventilated between 3 and 42 days (mean 15 days). Seventeen infants (77%) received extra oxygen until 1 to 28 weeks after birth (mean 12 weeks). None of the infants suffered from bacterial meningitis, but 6 (28%) went through a sepsis. Three infants (14%) suffered from a grade II, two infants from a grade III intraventricular bleeding. One of the infants with a grade II bleeding got a subsequent hydrocephalus.

EQUIPMENT

For EOAE recording we used the ILO88 (Otodynamics, London, software Version 3.0). This equipment is described in detail elsewhere *(Kemp et al, 1990; Chapter 3).*

PROCEDURES

The EOAE recordings were always done by the first author. Infants staying in hospital were examined weekly in the ward, lying in their incubator or crib. Hospital staff and parents were often present. At the neonatal outpatient clinic recordings were made when the infants had their regular follow-up visits, intended at 43, 53, and 66 weeks mean postconceptional age. The infants were lying on their parent's lap or in a baby-car/-chair, during the examination. Many infants were asleep or dozing, some were alert and others quite restless. None of the examination rooms was sound treated.

For each examination it was recorded whether it was made in the ward or at the outpatient clinic. A recording was considered technically successful either if 260 stimulus sequences had been accepted or if the condition of the patient did not allow further testing and, visually judged, a clear EOAE was present or clearly 'no EOAE' was present (and not to be expected if 260 stimulus sequences would have been accepted). In addition, the stimulus level of recordings showing no EOAE had to be above 71.5 dBSPL, otherwise the recording was scored as unsuccessful, or was restarted after repositioning of the probe or increasing the stimulus level.
Since unsuccessful recording attempts in the neonatal ward were merely counted, the number of unsuccessful recordings for each patient individually is unknown at this site. For recording attempts at the outpatient clinic unsuccessful recordings were also identified on patient.
For each infant included the following perinatal characteristics were scored: the birth weight, gestational age, Apgar score after 1 and 5 min., the umbilical pH and the maximal serum bilirubin. Furthermore, it was scored whether ototoxic antibiotics had been administered and how long the infant received ventilatory assistance. These variables represent the patient history prior to that examination.
At the time of the examination, the age and weight of the infants was registered, and whether the infants were naso-oesophageally intubated for food administration and/or received extra oxygen per naso, and/or were lying in an incubator. These variables represent patient condition at the time of the examination.
The postconceptional age at the moment of transfer to a secondary referral hospital, and at the moment of discharge from any hospital was recorded.

All recordings were stored on disk. Of each recording we stored data in a database on the probe type used, the stimulus level ('Peak'), the stability of the stimulus ('Stabil'), the artefact-rejection level ('Limit(peak)'), the measurement duration ('Test time'), and the number of responses acquired in quiet ('Quiet'). The response variables stored in this database are mentioned below (see 'Data processing').
No otoscopy, or impedance testing was done in the infants, nor were they systematically screened by BERA.

Table 2. Each row in table 2 displays many data on one of the 22 infants selected and the EOAE recordings made. The columns labelled 25 to 65 represent the postconceptional age class in which specific events for each infant occurred. The moment of birth is represented by a black square. The time period of ventilatory assistance with intubation is symbolised (V), and of extra oxygen per naso (O). It is displayed whether a recording is done while the infant was naso-oesophageally intubated for food administration (T), and while lying in an incubator (I). The moment of discharge from our hospital or transfer to a secondary referral hospital is represented by a thick left or right cell border. The moment of discharge from a secondary referral hospital is represented by a double line. Every EOAE recording attempt is represented by an 'E'. The visual EOAE scores are given as super- or sub-index with the 'E': 'absent or doubtful EOAE' (A), 'EOAE present' (P).

Infant number	Post-Conceptional Age in weeks											
↓	25	26	27	28	29	30	31	32	33	34	35	36
1					■ V (1)	V (3)	I T E^{A}_{P}	I E^{P}_{P}	I T E^{A}_{P}			
2		■ V	V	O	O	O	I T E^{A}_{A}	I E^{A}_{A}	I T E^{A}_{A}			
3								■ I E^{P}_{P}	I T E^{P}_{P}	I T E^{P}_{P}		
4					■ V (1)	O	I T O E_{A}	I T E^{P}_{P}	I T O E^{P}_{A}	I T E^{A}_{P}		
5								■ I E^{P}_{P}	I T E^{P}_{P}	I T E^{P}_{P}	I T E^{P}_{P}	
6								■ V (1)	I E^{A}_{A}	I T E^{A}_{A}	I T E^{P}_{P}	
7				■ V (1)	I E^{P}_{P}	V (2)	I E^{A}_{P}	I T E^{P}_{P}		T E^{P}	T E^{P}_{P}	
8				■ V (1)	O	O	I T O E^{P}_{P}	O	I T O E^{A}_{P}	I T E^{P}_{P}		
9					■ V (3)	O	I T O E^{P}_{P}	O	O	O	I T O E_{P}	E^{P}_{P}
10		■ V	V	V	O	O	O	O	O	T E^{P}_{P}	T E^{P}_{P}	
11						■ V (3)	I T E_{A}	I T E^{P}_{A}	I T E^{P}_{P}	I T E^{A}_{P}	I T E^{P}_{P}	I T E^{P}_{P}
12						■ V (4)	O	I T O E^{P}_{P}	O	I T E^{P}_{P}		
13				■ V	V	V	V	V	V	O	I T O E^{P}_{A}	O
14			■ V	V	V	V	V	O	O	O	O	T O E_{P}
15		■ V	V	O	O	O	I T O E^{A}_{A}	I T O E^{A}	I T O E^{A}_{A}	I T E^{P}_{P}	T E_{P}	T E^{P}_{P}
16			■ V	V	V	V	V	V	I T O E^{P}_{P}	T O E^{P}_{P}	O E^{P}_{P}	O E^{P}_{P}
17		■ V	V	V	V	O	O	O	O	O	O	I T O E^{A}_{A}
18		■ V	V	V	V	V	V	O	O	O	I T O E_{P}	I T O E^{A}_{A}
19		■ V	V	V	V	V	V	O	O	I O E^{A}_{A}	I T O E^{A}_{A}	T O E^{A}
20				■	V	V	V	O	O	O	I T O E^{A}_{A}	O
21	■ V	V	V	V	V	V	V	V	O	O	O	O
22		■ V	V	V	V	V	O	O	O	O	I T O E^{P}_{P}	T O E^{P}_{P}

N (EOAE present)	2	-	6	13	11	17	18	11
Mean Response Level (dBSPL)	13.9		11.8	11.7	12.2	14.2	14.2	15.6
Mean Response Reproducibility (%)	94		80	70	65	80	71	84
Mean Background Noise Level (dBSPL)	2.3		4.5	5.5	5.6	5.2	7.9	6.3

Mean Spectrum Level 1000-2350 Hz (dBSPL)	16.0		7.6	7.6	9.0	10.8	8.7	8.6
Mean Spectrum Level 2350-6250 Hz (dBSPL)	5.0		9.1	8.9	8.7	11.1	11.4	13.2
Difference (dBSPL)	11.0		-1.5	-1.3	0.3	-0.3	-2.7	-4.6

An unsuccessful recording is represented by a minus sign (-). The (visual) score for the right ear is superscripted, for the left ear subscripted. The extra column at the right, labelled 'M', shows the total number of successful recordings per infant, and for each ear separately as a super- or sub-index to 'M'. The four separate rows below the main table show the number of (visually scored) present EOAEs per age group (N), and the mean values of the EOAE response level, reproducibility, and background noise level after filtering the response above 1 kHz. At the bottom of the table three rows show mean spectrum level in dBSPL, again only in recordings showing a visually judged EOAE. The mean spectrum level between 1000 and 2350 Hz, between 2350 and 6250 Hz, and the difference between the low and high frequency energy content are given respectively.

The 22 infants were sorted by postconceptional age at the moment of discharge from (our) hospital, or transfer to a secondary referral hospital. This results in the early discharge group, i.e. infant number 1 to 11, and the late discharge group, i.e. infant number 12 to 22.

Post-Conceptional Age in weeks										Infant number	
37	38	39	40	41	42	43	46	54	65	↓	M
							E^{A}_{A}	E^{A}_{A}	E^{P}_{P}	1	12^{6}_{6}
							E^{P}_{P}	E^{-}_{-}	E^{-}_{-}	2	8^{4}_{4}
								E^{P}_{P}		3	8^{4}_{4}
							E^{-}_{P}	E^{P}_{-}		4	9^{4}_{5}
							E^{P}_{P}	E^{P}_{P}		5	12^{6}_{6}
							E^{P}_{-}	E^{-}_{P}		6	8^{4}_{4}
E^{P}_{P}					E^{P}_{P}			E^{P}_{P}		7	15^{8}_{7}
								E^{P}_{-}	E^{-}_{P}	8	8^{4}_{4}
							E^{P}_{P}	E^{P}_{P}		9	9^{4}_{5}
			E^{P}_{P}			E^{P}_{P}		E^{P}_{P}		10	10^{5}_{5}
I T E^{P}_{P}	I T E^{A}_{A}						E^{P}_{-}			11	16^{8}_{8}
E^{P}_{P}	E^{P}_{P}	E^{P}_{P}		E^{A}_{-}				E^{P}_{P}	E^{-}_{-}	12	13^{7}_{6}
O	T O E^{A}_{A}	T O E^{A}_{A}	O	O	O	O	O E^{P}_{P}		E^{-}_{-}	13	8^{4}_{4}
T O E^{P}_{P}	T O E^{A}_{A}	O E^{A}_{A}	O	O E^{P}_{A}	O	O	E^{P}_{P}	E^{P}_{P}	E^{-}_{P}	14	14^{6}_{8}
T E^{A}_{P}	T E^{P}_{P}	E^{P}_{P}		E^{P}_{P}			E^{P}_{-}		E^{-}_{-}	15	19^{10}_{9}
O	O	O	O			E^{P}_{P}			E^{-}_{-}	16	10^{5}_{5}
T O E^{A}_{A}	O	O	O E^{A}_{A}	O	O E^{-}_{-}	O	O	E^{P}_{P}		17	8^{4}_{4}
T O E^{-}_{A}	O	O E^{P}_{P}	O E^{P}_{P}	O	O E^{P}_{P}	O	O E^{-}_{-}			18	10^{4}_{6}
T O E^{-}_{A}	T O E^{A}_{-}	E^{A}_{A}		E^{A}_{-}	E^{A}_{A}		E^{A}_{-}	E^{-}_{-}	E^{-}_{-}	19	13^{8}_{5}
T O E^{A}_{P}	T O E^{P}_{P}	T E^{P}_{P}	E^{P}_{P}	E^{A}_{A}		E^{A}_{A}	E^{-}_{-}	E^{P}_{P}		20	16^{8}_{8}
T O E^{A}_{A}	T O E^{-}_{A}	O	O E^{A}_{A}	O	O	O E^{-}_{A}	O E^{-}_{-}	O E^{P}_{P}		21	8^{3}_{5}
T O E^{P}_{P}	O	O	O E^{P}_{P}	O E^{P}_{P}	O	O	O E^{P}_{P}	O E^{-}_{-}	E^{-}_{-}	22	12^{6}_{6}

12	6	8	8	5	4	4	15	23	4
18.4	17.4	18.1	17.0	15.3	23.3	25.8	19.1	20.2	12.2
83	80	90	87	76	96	99	84	86	38
7.3	9.5	5.4	6.6	6.3	7.6	3.6	9.3	8.3	11.8

13.3	15.3	17.0	14.4	11.7	20.9	19.8	16.6	18.6	10.1
15.9	13.8	14.4	13.7	12.4	20.2	24.1	16.1	16.5	7.0
-2.6	1.5	2.6	0.7	-0.7	0.7	-4.3	0.5	2.1	3.1

DATA PROCESSING

Age classification

In table 2 we used postconceptional age classes of whole weeks up to 43 weeks. Thereafter, a division into postconceptional age classes of 46 (44 to 48 weeks), 54 (49 to 59 weeks), and 65 weeks (59 to 70 weeks) was made. Some infants were examined two or more times in a time period of one age class. Then only the first recording session is presented in table 2.

Subjective EOAE score

The presence or absence of an EOAE was scored visually. Each response was subjectively scored as showing an 'EOAE', a 'doubtful EOAE', or an 'absent EOAE'. This manner of scoring was discussed in detail previously *(Chapter 3)*. Important factors in our manner of scoring are the response waveform, its reproducibility and the relative strength of the frequencies in the spectrum of the response, rising above the background noise. Our scoring method is tolerant of responses in which only part of the waveform is reproduced. Eventually, for data analysis, the 'doubtful EOAE' scores were counted as 'absent EOAE'.

Objective EOAE variables

After filtering each response above 1 kHz, with help of the ILO88 program itself, the response level, absolute reproducibility, and background noise level were obtained. Below 1 kHz the EOAE spectrum predominantly contains noise. We think filtering above 1 kHz is a rather safe method to facilitate visual EOAE scoring and to obtain objective reproducibility figures fitting well with a 40-50% 'Repro'-criterion for EOAE presence *(Kemp et al, 1986; Chapter 3)*. A comparable method of signal processing is done in the fast screening protocol of the more recent version of the ILO88 (software version 3.92).
We also computed the mean EOAE spectrum level between 1000 and 2350 Hz, and between 2350 and 6250 Hz in dB.

RESULTS

The rows in table 2 numbered 1 to 22 display data on the selected infants and the EOAE recordings made. The columns labelled 25 to 65 represent the postconceptional age class in which specific events for each infant occurred (see legends for explanation). In table 2, the 22 infants were sorted by postconceptional age at the moment of discharge from our hospital, or transfer to a secondary referral hospital. This elucidates a bisection in the population: the early discharge group, i.e. infant number 1 to 11, and the late discharge group, i.e. infant number 12 to 22. Nine of the infants who were discharged at a relatively low postconceptional age got ventilatory assistance for a few days only (range 1 to 18 days, mean 6 days). Six of them got extra oxygen, and if so, for a short period of time (1 to 7 weeks, mean 5 weeks). Consequently, the recordings could be made at low postconceptional ages. The infants who were discharged at a relatively high postconceptional age have all been ventilated, and for a longer period of time (range 4 to 56 days, mean 28 days). The recordings in these infants were done at a relatively higher postconceptional age. All of them got extra oxygen from 4 to 52 weeks (mean 18 weeks), and at birth most cases had a gestational age below the total group average of the selected 22 infants.

Analysis of the EOAE recordings was done after filtering the response above 1 kHz by use of the ILO88.
Since there are large intra-individual variations in EOAE results, the successful recordings made in four patients are shown in figure 1 to 4. The response waveforms, consisting of an A and a B trace are shown, vertically sorted by postconceptional age of the infant at the time of the recording. The dashed line at the beginning of the recorded waveform is the stimulus waveform. Above the total waveform to the right the 'I' (incubator), 'T' (naso-eosophageal tube), and/or 'O' (extra oxygen) patient data symbols as used in table 2 are displayed if applicable. Also the weight and postconceptional age of the infant is given here. In front of the waveform the stimulus level ('Stim'), response level ('Echo'), response reproducibility ('Repro'), and background noise level ('Noise') are shown. Behind the waveform the spectrum of the response and background noise are displayed, in white and black respectively, and related to the left Y-axis in dBSPL. The dashed line in the spectrum represents the stimulus spectrum, which is related to the dashed right Y-axis in dBSPL. The visual EOAE score is displayed above the spectrum (A or P).

Figure 1 shows the recordings of infant number 5, a boy born after 31.9 weeks gestational age, with a birth weight of 1345 g (table 1). Postnatally he needed no ventilatory assistance, or extra oxygen. A few days later EOAE recording could be started. As long as he was in our hospital he remained in an incubator, and except for the first recordings he also was naso-oesophageally intubated. The boy went home at the postconceptional age of about 39 weeks. Follow-up at the outpatient clinic could be done at 45.7 and 52.6 weeks postconceptional age. All recordings showed EOAEs. The strongest EOAEs were recorded at the outpatient clinic at 45.7 weeks. The EOAE spectral energy was relatively uniformly distributed. The spectral width of EOAE frequencies was rather constant from recording to recording.

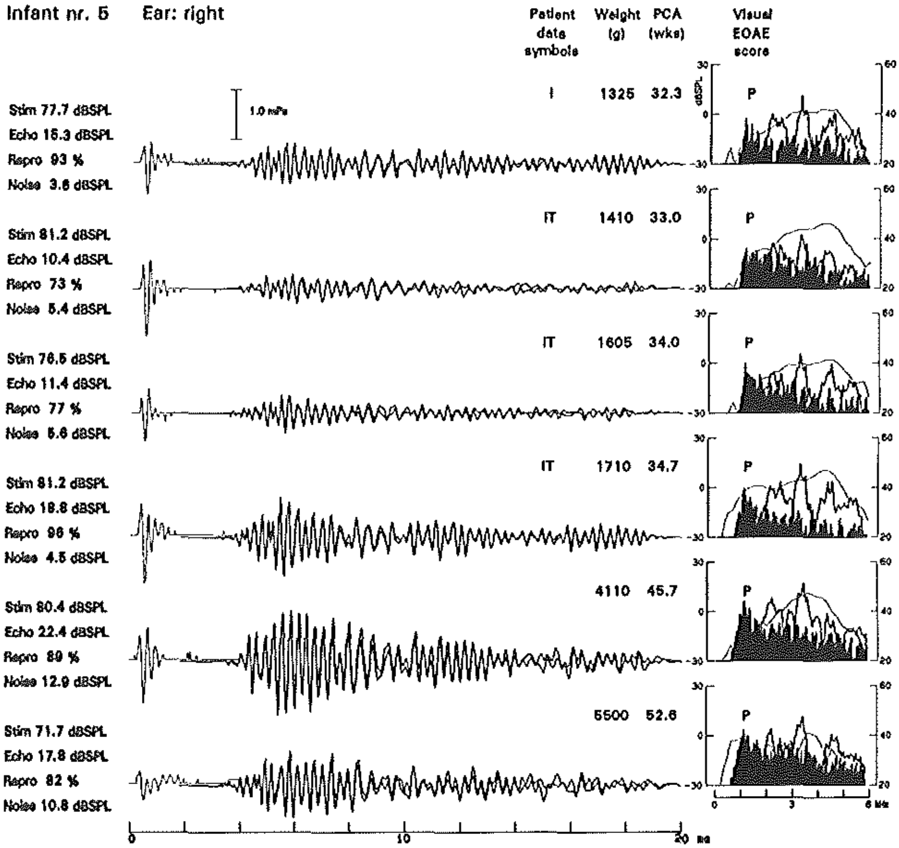


Figure 1A

Results of repeated EOAE recordings sorted by postconceptional age (PCA) in the right ear of infant number 5, who was born at a weight of 1345 g, after 31.9 weeks gestational age. See the text of the 'Results' for further explanation. The patient data symbols are discussed in the legend of table 2.

Figure 2 shows the recordings done in one of the male infants (nr.11). He was born after 30.1 weeks gestational age, which was above the mean for the subpopulation of 22 selected infants. His birth weight of 840 g was below the mean. Recording could already be started about one week after birth, because he needed to be ventilated after birth for 3 days only. At the time of the recordings the postconceptional age of the infant was between 31.4 and 44.9 weeks, the weight between 860 and 2935 g. All the successful recordings in the ward, 7 in the right and 8 in the left ear, were done at a constant patient condition, i.e. in an incubator, with a naso-oesophageal tube for food administration, and without extra oxygen per naso. At the outpatient clinic only a recording at 44.9 weeks postconceptional age was done, one week after discharge from a secondary referral

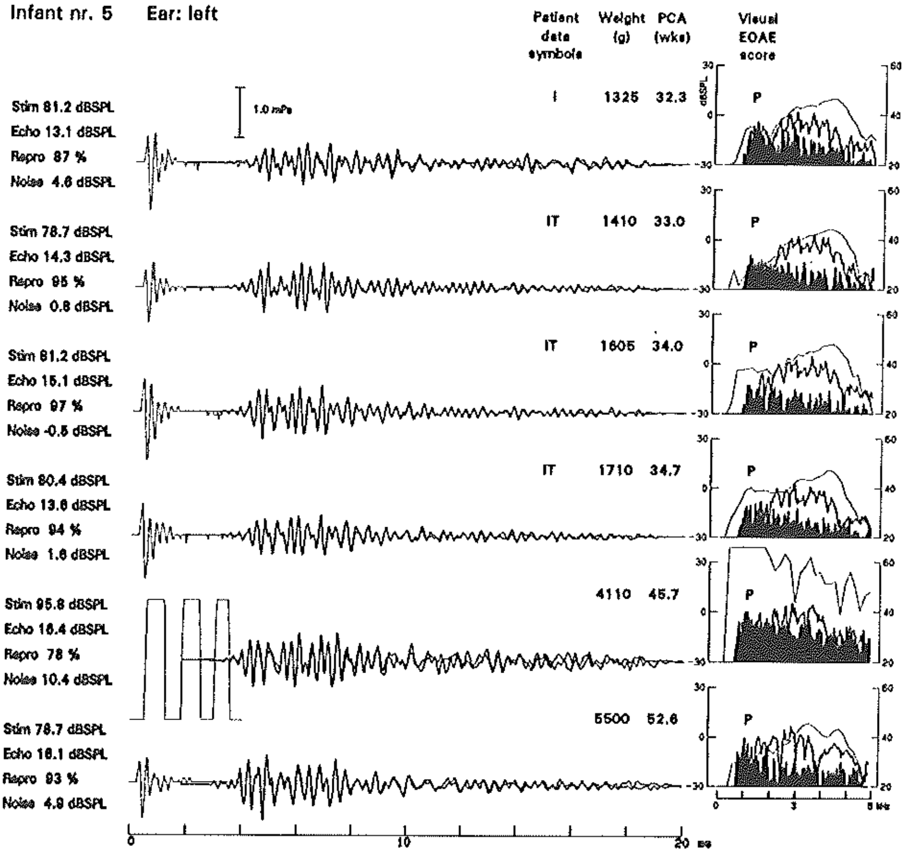


Figure 1B
Results of repeated EOAE recordings in the left ear of infant number 5.

hospital, and then successful only in the right ear. Both ears showed clear EOAEs most of the time. It is also clear that the strength of the emission was highly variable in time. Sometimes the emission was so weak that the visual EOAE score 'absent' resulted. We observed no systematic growth/decrease with age of response level, reproducibility, or background noise level from recording to recording. However, in both ears the first EOAE present was clearly less strong than the last. The recordings at the outpatient clinic showed a very high background noise level. The left ear showed a low level EOAEs with spectral energy above about 3 kHz. The right ear showed EOAEs with spectral energy above 3 kHz at first, but over the whole spectrum when recorded at 37.1 and 44.9 weeks postconceptional age. These EOAEs were also stronger than in the earlier recordings.

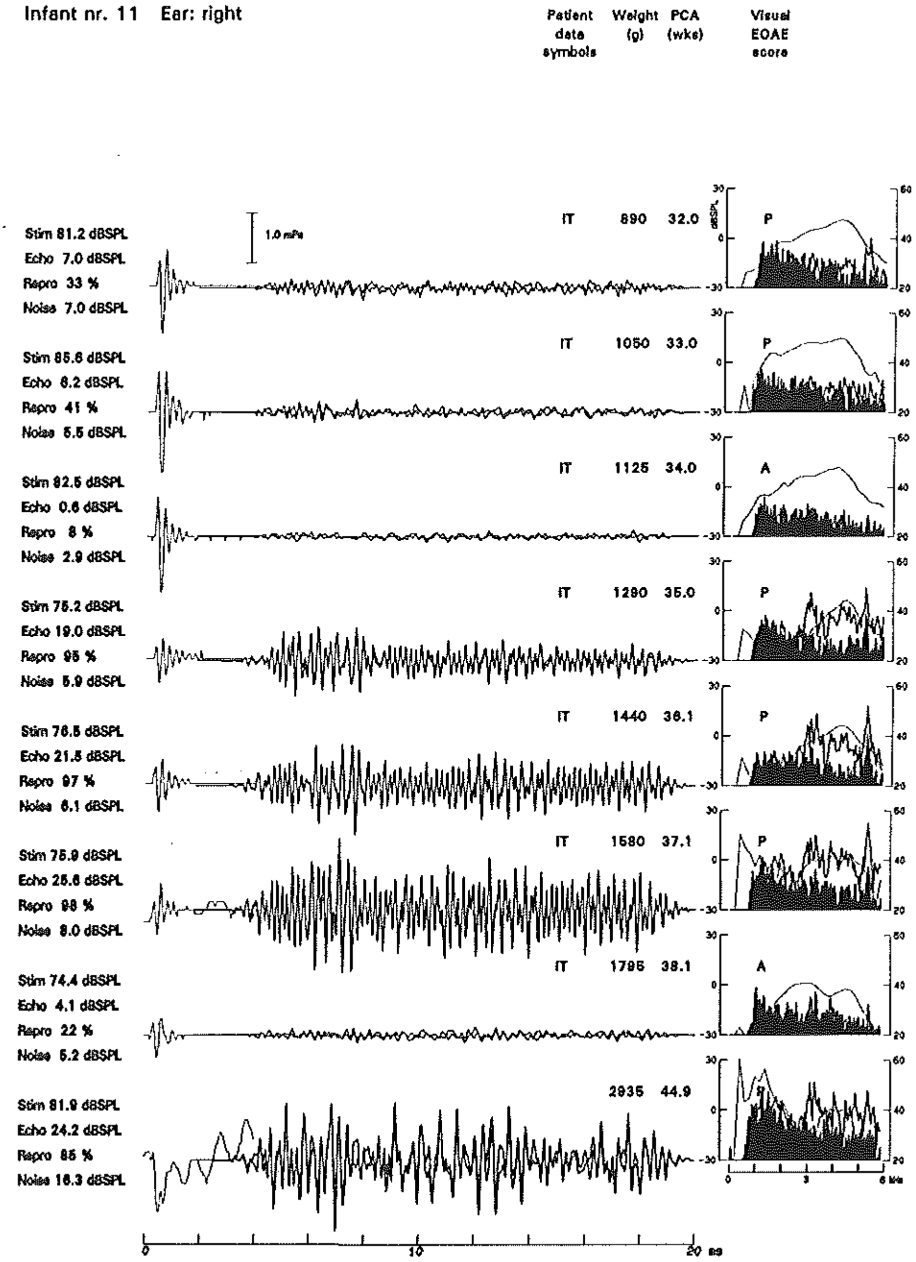


Figure 2A

Results of repeated EOAE recordings sorted by postconceptional age (PCA) in the right ear of infant number 11, who was born at a weight of 840 g, after 30.1 weeks gestational age.

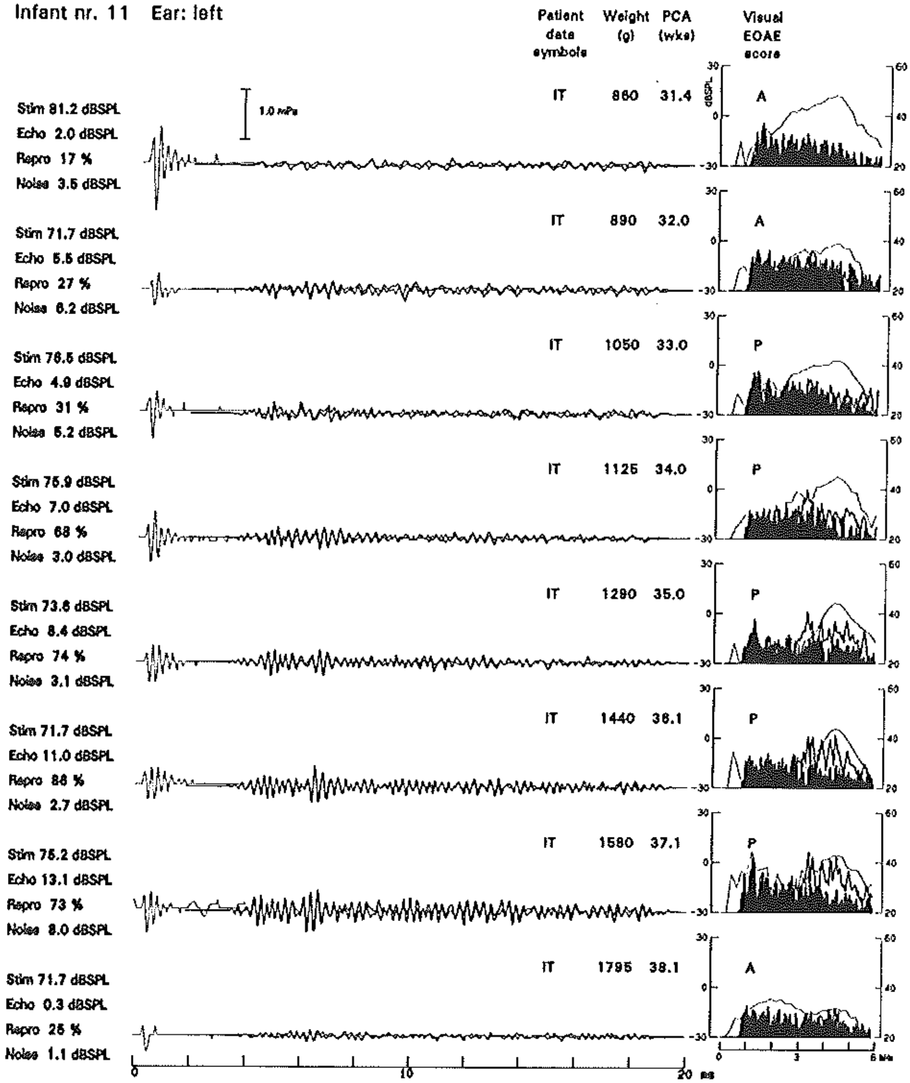


Figure 2B
Results of repeated EOAE recordings in the left ear of infant number 11.

Figure 3 shows the results of EOAE recording in infant number 17. This boy was born after a gestational age of only 25.6 weeks with a birth weight of 720 g. He had to be ventilated for 4 weeks. EOAE recording could not be started until 10 weeks after birth. He needed extra oxygen until 46 weeks postconceptional age. The first recording in the ward was done in the incubator. The first two were done while the infant was naso-

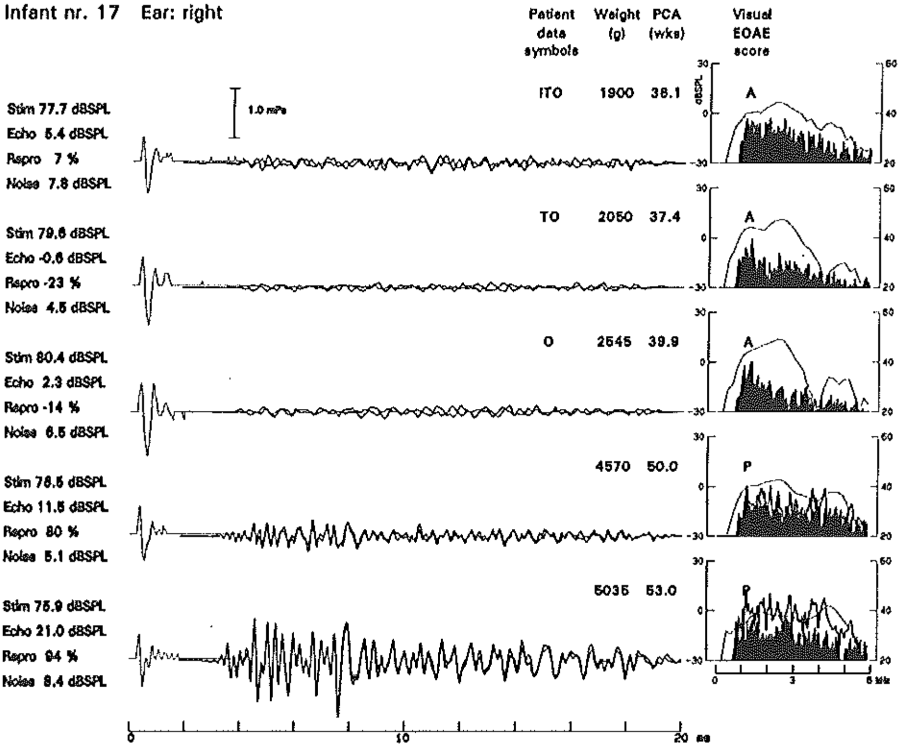


Figure 3A
Results of repeated EOAE recordings sorted by postconceptional age (PCA) in the right ear of infant number 17, who was born at a weight of 720 g, after 25.6 weeks gestational age.

oesophageally intubated. All three recordings made in the ward showed no EOAE. An outpatient clinic follow-up examination 2 weeks after discharge from hospital at 42.2 weeks postconceptional age was unsuccessful. For the first time, the EOAE proved to be bilaterally present at 50.0 weeks postconceptional age, at the outpatient clinic, and was still present at 53.0 weeks. The EOAEs showed low as well as high frequency energy.

Figure 4 shows the recordings done in infant number 20. He was born after 28.0 weeks gestational age, and had a birth weight of 1305 g. The recordings were done between the postconceptional ages of 34.9 and 51.2 weeks, and a weight between 2045 and 3785 g. The boy had to be ventilated from 28.6 to 31.6 weeks postconceptional age, because of a sepsis. Not until 7 weeks after birth (postconceptional age 34.9 weeks) the boy was stable enough for EOAE recording. The first bilateral recordings, and in the right ear also the second recording did not show an EOAE. During these recordings the boy received extra

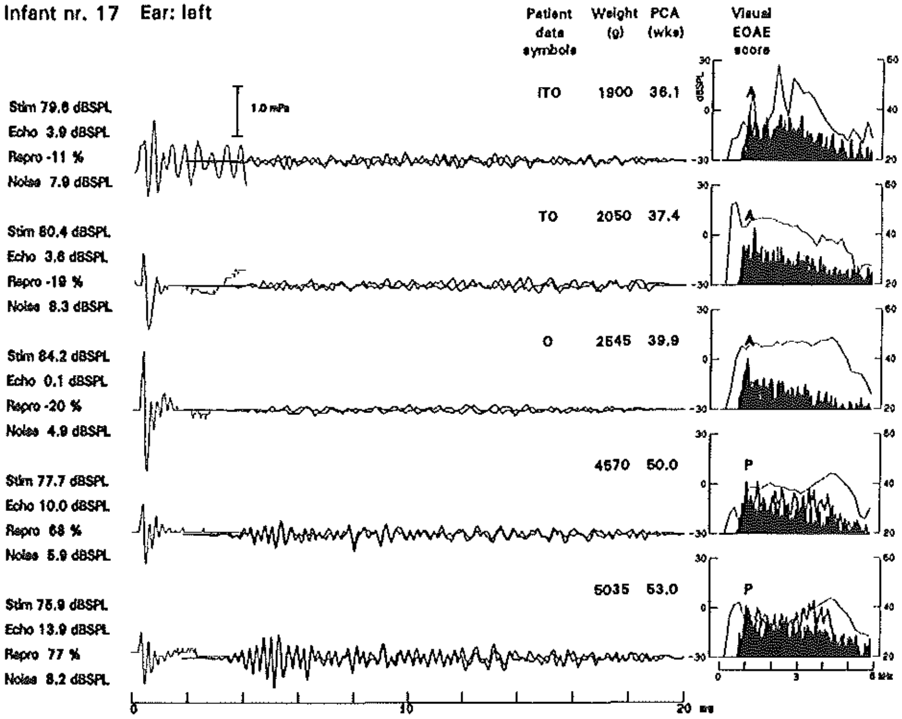


Figure 3B

Results of repeated EOAE recordings in the left ear of infant number 17.

oxygen per naso, and had a naso-oesophageal tube. At the first recording only, he was lying in an incubator. The EOAE showed up before the extra oxygen is stopped, or the feeding tube removed, i.e. at 36.5 weeks postconceptional age in the left and at 37.7 weeks postconceptional age in the right ear. At a postconceptional age of 40.6 weeks, the EOAE disappeared again bilaterally. A recording attempt at 44.8 weeks postconceptional age at the outpatient clinic (table 2), only one day after discharge from from our hospital, was unsuccessful bilaterally. We observed no clear growth of the response level with age, but the strongest EOAEs were recorded at the outpatient clinic at 51.2 weeks postconceptional age. Also the background noise level was stronger than in the recordings done in the ward. The spectral energy of the EOAEs in both ears of this infant was relatively uniformly distributed. In the recordings with low level EOAEs broad peaks above the background noise nearly covered the spectrum.

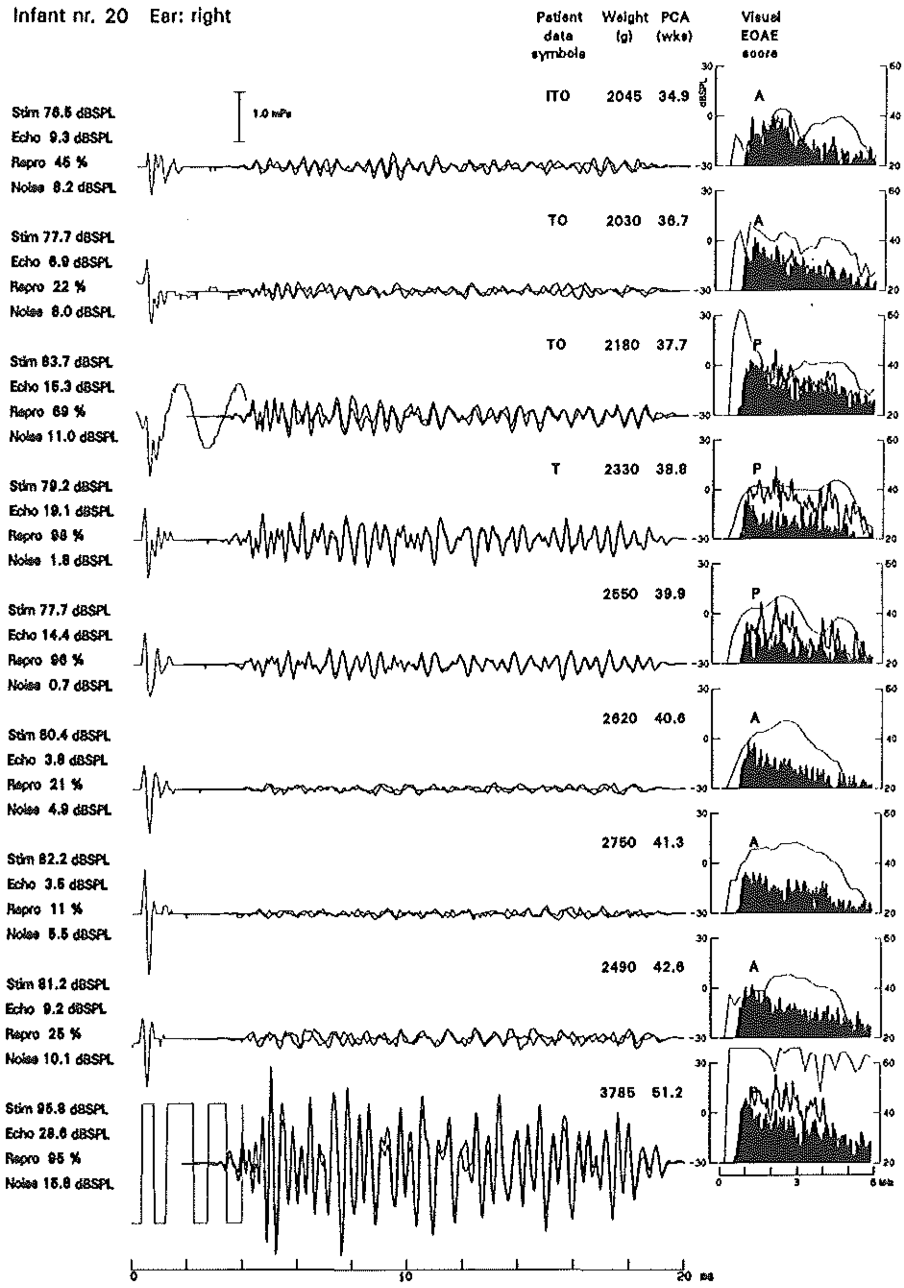


Figure 4A

Results of repeated EOAE recordings sorted by postconceptional age (PCA) in the right ear of infant number 20, who was born at a weight of 1305 g, after 28.0 weeks gestational age.

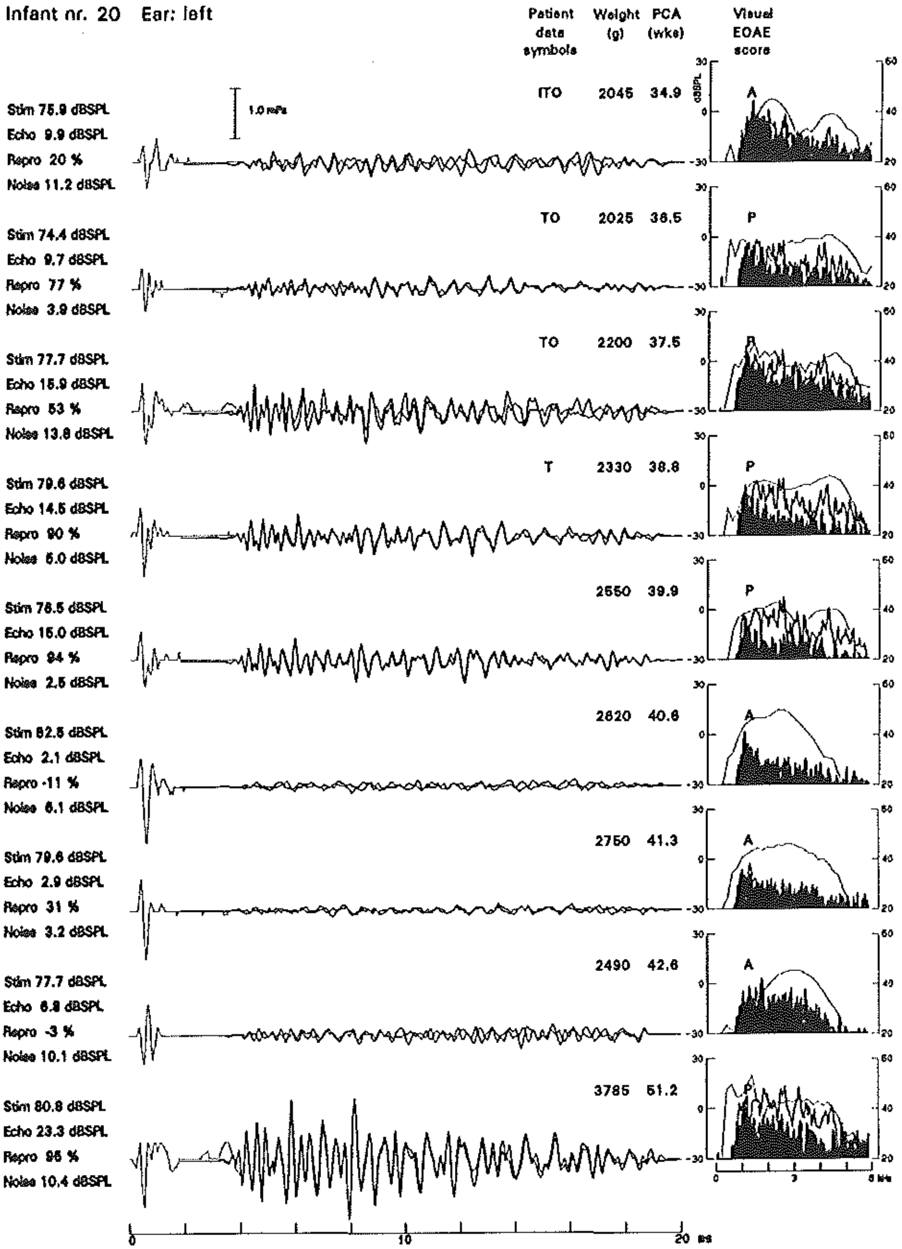


Figure 4B

Results of repeated EOAE recordings in the left ear of infant number 20.

BASIC EOAE FEATURES

In table 2 a clear increasing trend of the mean response level with age exists until about 43 weeks postconceptional age. No clear increase in mean response reproducibility with age can be observed. These figures were obtained from responses showing presence of an EOAE only. The EOAE recordings in figure 1 to 4 show that there is a large intra-individual and intra-ear variability in response level. In none of the examples shown a clear growth in response level exists. Also in the other 18 ears we found no clear growth in level with age. However, the strongest EOAEs were recorded at the outpatient clinic, so at a high postconceptional age.

The EOAE spectrum ranged from about 2 to 5 kHz in most ears. In the spectra of the low level EOAEs in an ear, about the same spectral width was covered by broad peaks. As described above, there appeared to be no clear intra-ear growth in response level with age, yet the first EOAEs recorded in an ear are often the lowest level ones. These less strong primary EOAEs showed only high frequency spectral energy, i.e. above about 3 kHz in 6 ears of 4 infants (figure 1). We found a primary EOAE with exclusively low frequency spectral energy (below 3 kHz) in 1 ear only. So, all the other ears showed EOAEs with a rather stable shape of the spectrum from 2 to 5 kHz over time. The three rows at the bottom of table 2 show that the mean spectrum level increases with age, both in the low frequency range (1000 to 2350 Hz), as well as in the high frequency range (2350 to 6250 Hz). Their difference is age independent.

EOAE PRESENCE

In a boy born at 28.3 weeks gestational age, and with a birth weight of 1400 g, an EOAE was present already at the postconceptional age of 29.4 weeks (table 2, nr.7).
One infant (nr.19) in this sub-population of the study never showed an EOAE. He was born after 26.1 weeks gestational age and had a birth weight of 835 g. The successful recordings were done at a postconceptional age between 34.2 and 43.8 weeks, while his weight was between 1685 and 3500 g. Above 43.8 weeks, at the outpatient clinic no successful recordings could be done. At 46.2 weeks postconceptional age an BERA showed no cochlear abnormalities. A small conductive hearing loss could nevertheless not be excluded.
In 15 ears (34%) of 9 infants of this selected study EOAEs were present in all recordings done.

DISCUSSION

DATA REPRESENTATIVITY

This longitudinal study in VLBW infants with EOAE recording showed a less than optimal sequencing of successive recordings. The testing had to go along with the normal clinical routine, which determined the characteristics of this population. For instance the 'stable' infants were transferred to other hospitals sooner than the others, and in some cases the outpatient clinic follow-up visits were not made in our hospital, but in a hospital nearby home. The early transfer to other hospitals and shorter follow-up at the outpatient clinic of the 'better' infants resulted in longer intervals between recording and a shorter or less complete follow-up than intended.

Since we required at least 4 bilateral recordings in the group of 22 selected infants, this group may have been a negative selection with relatively few of the 'better' infants. The selected infants indeed had a slightly lower mean gestational age and birth weight than the initial population of 144 infants. Their Apgar scores were comparable. Of the total population admitted to our hospital 33% had a birth weight below 1000 g. This proportion was much higher in the group of 22 selected infants (13=59%). The period of ventilatory assistance in the selected group of infants with a birth weight between 1000 and 1500 g was slightly longer than in the infants in the total population. The incidence of bacterial meningitis, intraventricular bleeding, and hydrocephalus was not significantly different between the selected and total group.

Another reason for missing EOAE data is the fact that the EOAE recording in the total population of VLBW infants was much more difficult than in healthy newborns *(Chapter 6)*, which resulted in a lower success rate of recording.

Since the number of unsuccessful recordings for each patient individually in the ward is unknown we calculated the success rate for the recordings made from 44 weeks postconceptional age and higher only. Seven ears of four infants were never successfully tested at the outpatient clinic. Restricting analysis to the recording attempts in the postconceptional age class of 46 and 54 weeks, we found a success rate of 69%, which is in accordance with the results of cross-sectional data analysis of 64 to 68% in these age classes *(Chapter 6)*. A decrease in success rate of EOAE screening with age and between ward and outpatient clinic recordings was also reported by Webb and Stevens *(1991)* and Stevens et al *(1989)*. Uziel and Piron *(1991)* found a lower success rate in VLBW infants compared with other neonatal intensive care infants. The success rate in this longitudinal data analysis was lower in the late (60%=18/30) than in the early (76%=26/34) discharge group. The attempts were more frequently unsuccessful in ears of infants in the late discharge group, who were discharged from our hospital only recently before recording. We cannot analyze whether a change of habitat indeed influenced the success rate unfavourably since the early discharge group infants were seldom examined shortly after discharge. An explanation for the lower success rate in the late discharge group may have been the fact that infants with a birth weight and gestational age at the lower end of the range were relatively the most stressed and restless infants, maybe especially shortly after a change of habitat.

Summarizing the data representativity we note that the subgroup of 22 selected infants appeared representative for the total group of VLBW infants admitted to our hospital. Comparing the success rate in the cross-sectional data analysis and in this longitudinally analyzed subgroup, representativity is also observed.

BASIC EOAE FEATURES

We found that the mean response level per age group showed an increasing trend with age until about 43 weeks postconceptional age. This maturational effect can be caused by changes in middle and/or inner ear status. Regarding the possibility that the inner ear maturation may have been reflected in the EOAE characteristics, we also would have expected to find higher frequency emissions initially, and low frequency emissions in the later recordings. This is based on the findings in literature that the anatomical development of outer hair cells and their efferent innervation appears to start in the basal turn, and progresses apically *(Anniko, 1985; Pujol, 1985)*. On the other hand, behavioral threshold measurements show responses in the lower frequencies first *(Spetner and Olsho, 1990)*. We observed an increase in the mean spectrum level in the low (1000 to 2350 Hz) as well as the high frequency range (2350 to 6250 Hz) with age, but the growth rates were not significantly different between the two frequency ranges. In 6 ears however, like in figure 2, we did find the lower level initial EOAEs to show mainly high frequency energy. Inner ear maturation, starting in the basal turn, may cause stronger high frequency emissions first. It may be that in these six ears we did see a reflection of the maturation of the inner ear as changes in EOAE spectrum, containing more low frequency energy in the later recordings. We did not find this EOAE spectrum changes in the other ears. This means that these changes did not occur in all ears, or we may well have been to late in starting the recordings to monitor this EOAE spectral changes. After all, we did find a broad spectrum EOAE in one boy of 29.4 weeks postconceptional age. Although, the effect cannot be proven in our material, it may be that in a laboratory condition, in a silent room with a good control of the stimulus spectrum, definitive evidence for inner ear maturation in selected very preterm infants can be found.

Maturation of the inner is however not the only reason causing mainly high frequency EOAEs. The middle ear transfer may be better for higher frequency emissions than for lower frequency emissions. We cannot discuss nor exclude this possibility, since little is known about the middle ear transfer, especially for neonates. Also reduced low frequency EOAE energy may be caused by a very leaky fit of the probe *(Kemp and Ryan, 1991)*. We did always our very best in probe fitting, to accomplish the best stimulus waveform and spectrum. If the stimulus waveform and spectrum were bad nevertheless, even after multiple cleaning and repositioning of the probe, we think that this was most probably caused by the characteristics of the external/middle ear, and not due to our lacking probe fitting ability. Besides, this cause of low frequency energy loss is not expected to be age dependent.

The mean response reproducibility did not show an increase with age. In fact the mean reproducibility reflects our method of scoring, which is described extensively in our previous papers *(Chapter 3; Chapter 6)*. So, an increase in response reproducibility was not to be expected. The stronger EOAEs at about 40 weeks postconceptional age showed also a slightly higher mean response reproducibility.

EOAE PRESENCE

Although determination of the EOAE presence was no primary aim of this longitudinal study, we determined the mean presence until 43 weeks postconceptional age, and for the age classes 46 to 65 weeks postconceptional age. The overall mean EOAE presence until 43 weeks postconceptional age was 63% (125/198). It amounted to 74% (64/86) and 54% (61/112) in the early and late discharge group, respectively. The mean EOAE presence in the age classes 46 to 65 weeks postconceptional age was 90% (43/48). This amounted to 86% (25/29) and 95% (18/19) in the early and late discharge group, respectively. In the cross-sectional data analysis we calculated an overall EOAE prevalence for inpatients of 71% and for outpatients of 91%. These figures are more or less comparable to the overall presence until 43 weeks postconceptional age (63%), and in the age classes 46 to 65 weeks postconceptional age, respectively. So, comparing the EOAE presence figures between this study and the cross-sectional data analysis, again the selected subgroup appears representative.

In the selection of 22 infants, the youngest 'stable' infant we were able to examine with EOAE recording was 29.4 weeks postconceptional age. We found clear EOAEs with a response level of 11.8 and 15.9 dBSPL, and a reproducibility of 94 and 93% in the left and right ear respectively. The cochlea is able to produce an EOAE at this postconceptional age and so, probably, even at a lower age.

In this population of 22 selected infants at high risk for hearing impairment we found an EOAE in 95% (21/22) of the infants, although we were unable to record the EOAE in every recording attempt. We found an 'absent EOAE' in all recordings in one infant only.

Other studies recorded EOAEs at the time of the infants' discharge, and repeated this three months later if the infants did not pass the first test *(Webb and Stevens, 1991)*. Yet, this study showed (table 2) that in the recordings done right before discharge, we found an EOAE in 26 (59%) ears of 14 infants. Caused by the changes in EOAE scores, in another 9 (20%) ears of 6 infants, an EOAE was found to be present only at an earlier occasion. These 9 ears were about equally distributed over the early and late discharge groups. In our hospital there appears to be no reason to wait with screening of VLBW infants till discharge.

RELATIONS BETWEEN EOAEs AND PATIENT CONDITION

We found no systematic growth in EOAE level with age in the individual ear/infant. Before the postconceptional age of about 40 weeks, the EOAE level was strongly variable. Yet, in accordance with our cross-sectional data analysis in VLBW infants *(Chapter 6)* the strongest EOAE in almost all ears was recorded at a high postconceptional age in the outpatient clinic. In the early discharge group the period in which the EOAE level probably increased may have been missed, because the monitoring has not been complete from the moment of discharge to the first outpatient clinic follow-up recording.
Since the EOAE response level and EOAE presence are closely related, we were not surprised to find that in the ward the visual EOAE score varied strongly in 41% of the ears tested (18 ears (of 11 infants), table 2), when the same ear was examined repeatedly (see also figures 2 and 4). The ears with changing EOAE scores were tested on average once more (5 vs. 4) than ears with constant visual EOAE scores. In 9 (20%) ears of 5 infants an 'absent EOAE' was recorded in every recording done in the ward. In the remaining ears of the total group, i.e. 17 (39%) ears of 10 infants, all recordings in the warded show an EOAE. At the outpatient clinic 33 of the 38 successfully tested ears constantly showed an EOAE present in the successful recordings done at the outpatient clinic. One ear constantly showed an 'absent EOAE' at the outpatient clinic (nr.19, right).

Regarding the patient condition we observed that the EOAE may disappear unexpectedly (figure 2, table 2) in spite of unchanged patient condition variables. Changes in patient condition variables on the other hand caused no direct effect on the visual EOAE score (figure 1). However, we found that the late discharge group of infants were more likely to show an 'absent EOAE' in every EOAE recording (table 2, infant nr. 2, 13 (unilateral), 17, 19, 21) done in the ward. The overall EOAE presence was also lower (54%) in the late compared to the early discharge group (74%). In accordance with our findings, Webb and Stevens *(1991)* also reported a negative relation between gestational age and EOAE prevalence for inpatients. Apparently factors, like low gestational age and long period of ventilatory assistance are important in influencing the EOAE presence. In the cross-sectional data analysis of initially the same data *(Chapter 6)*, we found a lower EOAE prevalence in ears of infants receiving extra oxygen per naso, than in ears of infants who were not. This longitudinal study showed that no use of extra oxygen is no guarantee for a present EOAE. The usage of extra oxygen per naso was relatively high among infants constantly showing an 'absent EOAE', but these were also the ones born with a low birth weight and gestational age. Likely, the receipt of extra oxygen per naso solely is not important for screening.

The most likely cause for disappearance of the EOAE, or a decrease of the response level, is change in middle ear function. Unfortunately, we were unable to score the middle ear function, yet the incidence of (transient) middle ear effusion is known to be high in VLBW infants *(Eggermont and Salamy, 1988; Jacobson and Morehouse, 1984; Balkany et al, 1978)*. Balkany et al *(1978)* found a relation between a longer period of ventilatory assistance and middle ear pathology. Since the late discharge group needed a longer period of ventilatory assistance, and a more frequent and longer time period of extra oxygen per naso this may have resulted in a reduced middle ear function, and therefore disappearance of the EOAE. This is a possible explanation for the lower EOAE presence in the late discharge group. Kennedy et al *(1991)* reported 2 cases with an 'absent EOAE'. In spite of a normal immittance test these infants appeared to have a mild, but persistent conductive hearing loss. This suggests that EOAE presence is very sensitive to conductive hearing loss, and likely so to (transient) middle ear effusion. This may explain why we found no EOAEs in one infant in whom an BERA showed no cochlear abnormalities, but a possible small conductive hearing loss could not be excluded.

We think that changes in middle ear function caused the large variations in EOAE response level and obscured the true increase in response level in the individual ear or infant.

At the outpatient clinic the visual EOAE scores virtually did not vary. In most cases we were either unsuccessful in making an EOAE recording or the successful recording did show an EOAE. At this test site and postconceptional age, the EOAEs were stronger, causing a higher and more stable EOAE presence than in the ward.

CONCLUSION

1- The EOAE can be recorded at a postconceptional age as low as 29.4 weeks.

2- In this selected group of VLBW infants the mean EOAE level appeared to increase with age until about 43 weeks postconceptional age. Some VLBW infants showed only high frequency energy in the EOAE spectra recorded at low postconceptional ages, while the later recordings showed gradually more low frequency energy. Future research might uncover whether these changes are a reflection of ear maturation.

3- The strength of the EOAE, and the EOAE presence in the ward, i.e. before a postconceptional age of about 40 weeks, was strongly variable. We think the high prevalence of (transient) middle ear effusion in VLBW infants probably is the cause. At the outpatient clinic, at higher postconceptional ages, the stronger EOAEs had a more stable presence.

4- An overall EOAE prevalence of 83% (after a single recording per infant) resulted from a previous cross-sectional study data analysis in VLBW infants *(Chapter 6)*. In this study based on repeated recordings the EOAE presence increased to 95% (42/44 ears).

CHAPTER 8

GENERAL DISCUSSION AND CONCLUSIONS

As described in the introduction of this thesis the click-Evoked Oto-Acoustic Emission (c-EOAE) is a sound originated from the cochlea after stimulation of the ear with a click. Like other types of otoacoustic emissions the c-EOAE is a sound unique to the normal hearing process and absent in ears with moderate to severe loss of sensitivity to sound. Favourably, in normal ears the prevalence of c-EOAEs is almost 100%. In addition, the c-EOAE recording is easy in adults. Spontaneous Oto-Acoustic Emissions (SOAEs) are pure-tone like sounds generated by the cochlea without any stimulation at all. SOAEs, which are detectable in 30% of the normal hearing adult ears, can be synchronized by a stimulus and then they show up in the c-EOAE recording.

The c-EOAE recording could possibly become a viable method for screening the ear function in newborns. To evaluate this possibility, aspects of c-EOAE recordings found in about 1000 ears of healthy newborns, shortly after birth and using commercial equipment, were studied. In a population of very-low-birth-weight (VLBW) infants, at risk for hearing disability, the aspects of c-EOAE screening as well as any possible maturational changes in the c-EOAE features were described.

BASIC ASPECTS OF C-EOAES

Healthy newborns

Soon after starting the study in about 1000 ears of healthy newborns we found an increasing trend in c-EOAE level with age in the first days post partum *(Chapter 2)*. The growth of the c-EOAE level in the first days post partum is important for the use of c-EOAE recording as a screening test, and was studied more elaborately *(Chapter 3)*. Twelve healthy newborns were examined daily by c-EOAE recording 3 to 8 times in the first week of life. For each ear the response level data against age were fitted with a simple saturating exponential growth function. The growth period of the c-EOAE level appeared to vary strongly between individuals and no relation between the growth period of the c-EOAE level and the final level was found. Within infants however, the left-right ear correlations for both, the growth period and the final response level were high. Predominantly, the c-EOAE level changes occurred between day 0 and day 2 after birth. The age at which the response level reached at least 95% of its final value was 2 days in 50% and 5 days in 80% of the ears tested. The calculated final response levels varied between 10.0 and 34.3 dBSPL (mean 19.7 dBSPL).

The inner ear was less likely to have caused the growth in c-EOAE level in a time period of only a few days. Although we have only indirect evidence, we think that the growth in level was related to the middle ear clearance of amniotic fluid in the first days post partum. Some researchers think that debris in the external ear of newborns can abolish the c-EOAE *(Chang, 1993)*. They reported a higher prevalence of (stronger) c-EOAEs after cleaning the ear canal. However, the time interval between the first and second examination was not specified, and we can therefore not judge whether the effect was indeed due to cleaning the ear canal or simply due to waiting. Without cleaning we too found a higher prevalence of (stronger) c-EOAEs at an examination at least one day after the first one *(Chapter 2)*.

When a click stimulus is successful in synchronising a SOAE, a sharp peak will show up in the c-EOAE spectrum at the frequency of the SOAE. Shortly after starting our study in healthy newborns we observed frequent occurrence of these sharp peaks in the c-EOAE spectra. In addition to the c-EOAE recording we made a SOAE recording, i.e. a frequency analysis of sounds present in the ear canal without any acoustic stimulation of the ear, in 176 consecutive ears of healthy newborns *(Chapter 5)*. We found a SOAE prevalence of 78%, which was significantly higher than the figure of 30% reported in adults. Still, the noise floor of our equipment was relatively high compared to other studies. Since the SOAE prevalence is influenced by the noise floor and sensitivity of the equipment we proposed to report on the SOAE prevalence with specification of an absolute reference level. Thus, we found a prevalence of SOAEs stronger than 20 dBSPL of 20% in healthy newborns, while such strong emissions are virtually absent in adults. We hypothesized that a 100% SOAE prevalence can be found in healthy newborns if a noise floor, and concomitantly a reference level of -10 dBSPL can be effected.
The implication of the presence of SOAEs is still unclear, but the phenomenon is very interesting in the light of analyzing the cochlear physiology. Since SOAEs can influence the c-EOAE recording, aspects of SOAEs in healthy newborns were studied. Our data revealed that the SOAE prevalence, the mean number of SOAEs per ear, as well as their strength was higher in newborns than in adults. The tendency for the stronger presence in the right ear and in females *(Zurek, 1981; Strickland and Burns, 1985; Lonsbury-Martin et al, 1990b; Bilger et al, 1990; Burns et al, 1992)* was proven to be already present in newborns.

In all healthy newborns included the c-EOAE level ranged between 1.6 and 38.6 dBSPL (mean 20.2 dBSPL), which is significantly higher than we (range 2.7 to 20.6; mean 12.8 dBSPL) and other researchers found in normal hearing adult ears *(Chapter 4)*. Bray and Kemp *(1987)* suggested that the smaller ear canal volume in newborns could explain for this difference. We showed that the higher c-EOAE levels in newborns mainly resulted from the frequent occurrence of strong SOAEs *(Chapter 5)*. This relation was qualitatively also expressed in previous reports on EOAE and SOAE prevalence in infants, children, and adults. In infants younger than 18 months, in children and in adults, Bonfils et al *(1989)* observed a decrease in SOAE prevalence with age. In children of 6 to 12 years and in adults, Strickland found comparable SOAE prevalences. In agreement with the EOAE level and SOAE presence relation, Norton and Widen *(1991)* observed the greatest decrease in EOAE amplitude in children between the ages of 1 and 7 years. Summarizing, a decrease in c-EOAE level appears to be concomitant with a decrease in SOAE prevalence and this seems to occur in the first 6 years of life.

The frequency content of the c-EOAE spectrum in healthy newborns appeared to be skewed towards the higher frequencies (>2kHz) *(Chapter 4)*. 70% of the SOAE frequencies in healthy newborns were above 2 kHz *(Chapter 5)*. This is in contrast with findings in adults, whose c-EOAE spectrum content and SOAE frequencies are mainly between 1 and 2 kHz *(Zurek, 1981; Schloth, 1983; Kemp et al, 1986; Cianfrone, 1986; Dallmayr, 1985; Rebillard et al, 1987)*. In literature it has been suggested that differences in the middle ear transfer function between newborns and adults can explain for these differences. Yet, little is known about the middle ear transfer in newborns and it's maturation. We think that a cochlear origin of the change in frequency content of OAEs with age can not be excluded as yet.

Very-low-birth-weight (VLBW) infants

Knowing that the c-EOAE level increases in the first days post partum in healthy newborns, probably because of amniotic fluid clearance from the middle ear, we made the earliest c-EOAE recording in VLBW infants at least 4 days after birth. The 144 infants included were between 29 and 66 weeks postconceptional age at the time of recording *(Chapter 6 and 7)*. The c-EOAE data revealed that the c-EOAE level in VLBW infants was significantly lower than in healthy newborns, although the levels in ears of VLBW infants older than about 40 weeks postconceptional age approached those of healthy newborns *(Chapter 6)*. We succeeded in recording a c-EOAE in a VLBW infant of only 29.4 weeks postconceptional age. In a longitudinal analysis we found no monotonous individual growth of c-EOAE level with age. But the mean level per age class did show a steady growth until about 40 weeks postconceptional age *(Chapter 7)*. So, a developmental increase of c-EOAE level in VLBW infants existed that was not recognized in the individual ear because of transient strength dips. The most plausible cause of the strength dips are transient middle ear dysfunctions, which are known to be frequently present in VLBW infants. Infants who received ventilatory assistance for a longer period of time are particularly prone to middle ear dysfunction *(Balkany et al, 1978)*. Unfortunately, we had no opportunity to determine the middle ear function. Consequently, we cannot prove the middle ear dysfunctions and we are also unable to rule out developmental middle ear changes as a basis for the growth of mean c-EOAE level until 40 weeks postconceptional age. Developmental changes in the inner ear are a possible explanation for the steady growth in mean level too.

Like in healthy newborns the c-EOAE spectra of VLBW infants contained much high frequency energy, compared to adults. The growth in mean spectrum level was not significantly different between the low and high frequency range *(Chapter 7)*. Some ears however, showed only high frequency spectral energy in the early c-EOAE recordings, while the later recordings showed low frequency energy as well. This developmental change of the c-EOAE spectrum from strictly high to gradually more lower frequency content in a subgroup of VLBW infants is in agreement with the statements in literature that the cochlea matures from the basis towards the apex. We may well have detected a reflection of inner ear maturation in the c-EOAE recording. Again, middle ear changes can account for the c-EOAE spectrum changes as well. Due to changes in middle ear function, the transfer function for high frequency sounds may have been better at the early recordings than at the late ones.

Future studies may provide extended knowledge about the developmental changes in OAE frequency content, c-EOAE level and SOAE presence from (premature) birth into adulthood. Attempts should be made to distinguish between effects due to middle and to inner ear development.

ASPECTS PERTAINING TO NEWBORN HEARING SCREENING

SUCCESS RATE OF C-EOAE RECORDING

Healthy newborns

The c-EOAE recording is always successful in a cooperative adult. In healthy newborns it was more difficult to acquire a successful recording *(Chapter 4)*. Still, only 4% of the ears had to be retested because of a technical test failure, and a second attempt was always successful. So, the success rate of c-EOAE recording in healthy newborns at the well baby ward in the first week of life is acceptable for screening purposes.

VLBW Infants

On the assumption that the success rate in VLBW infants would be more or less comparable to the success rate in healthy newborns we only counted the unsuccessful recordings done in VLBW infants *(Chapter 6)*. Thus, the unsuccessful recordings were not identified on patient. In the course of the study in VLBW infants it became clear however, that these infants were much more difficult to test than healthy newborns. Not only the noisier environment in which these infants had to be tested, i.e. the neonatal high care unit, and the outpatient clinic, but also the restlessness of the infants themselves disturbed the recording. Afterwards we regretted that the unsuccessful recordings in the ward were not identified on patient, since that possibly might have enabled us to draw some conclusions about specific characteristics of the infants tested unsuccessfully. Fortunately, we have been able to identify the unsuccessful recordings done in outpatients retrospectively. Yet, we could only present "success rate figures" in VLBW infants that are based on repeated recordings in the same infants, but we came forward with indirect evidence that figures were not far off the mark *(Chapter 6)*. Overall, the success rate in VLBW infants amounted to 72%. In the ward 86% of attempts were successful against 60% of attempts at the outpatient clinic. At the outpatient clinic this figure decreased with age from 64-68% until 3 months to 33% at about 6 months corrected age. We could not find any significant relation between the success of the recording and perinatal patient data, the birth weight and gestational age among other things. Obviously, the older infants were awake during recording more often. In addition, an increase in cerumen production necessitated frequent cleaning and repositioning of the probe which caused extra distress before the recording could be started.

In the longitudinal data analysis *(Chapter 7)* we noted that the success rate was lower in infants who were tested at the outpatient clinic just shortly after discharge from hospital. Since these were also the infants born at a relatively low gestational age and birth weight, we could not differentiate whether a change of habitat solely or also the perinatal conditions of the infants caused the lower success rate.

Concluding we can state that the success rate in VLBW infants is test site dependent and decreases with age between about 0 to 3 months and 6 months corrected age.

We think a decreasing trend in success rate should be expected to occur in healthy newborns as well. Engdahl et al *(1993)* who recorded c-EOAEs 3 to 4 days after birth and repeated the recording in about 30 healthy newborns at 3, 6 and 12 months of age, indeed reported that the success rate of c-EOAEs decreased with age. So, as it comes to the success rate we recommend to screen early, preferably before the age of 3 months.

C-EOAE PREVALENCE

Healthy newborns

Preliminary data in healthy newborns *(Chapter 2)* revealed that the response level and consequently the c-EOAE prevalence increased with age the first days post partum. Hence, newborns should not be screened too soon after birth to facilitate c-EOAE detection and reducing the number of ears failing to show a c-EOAE. In the total population of healthy newborns examined in this study we found that the c-EOAE prevalence increased from 78% in ears from infants younger than 36 h of age to 99% in ears of infants older than 108 h *(Chapter 4)*. As discussed in the 'basic aspects' section about the c-EOAE level, we think the prevalence is age dependent due to middle ear clearance of amniotic fluid in the first days post partum.

Concluding, several days after birth the c-EOAE prevalence in healthy newborns is satisfactorily high for screening.

VLBW Infants

In our sample of VLBW infants, the overall c-EOAE prevalence was 83% *(Chapter 6)*. However, the prevalence was significantly lower in the ward (71%), for infants up to 40 weeks postconceptional age, than for the older infants examined at the outpatient clinic (91%). Our longitudinal analysis in a subgroup of VLBW infants *(Chapter 7)* revealed that like the individual c-EOAE level, the c-EOAE presence in an individual ear was highly variable until about 40 weeks postconceptional age. This resulted in a low mean c-EOAE prevalence in the ward. As discussed above we think that (transient) middle ear dysfunction is the major confounding factor causing this low c-EOAE prevalence. When the infants were older the prevalence was much higher (91%), but still not as high as found in healthy newborns.

In a subgroup of 22 VLBW infants *(Chapter 7)* we found a c-EOAE presence of 95% after repeated recordings, which shows that screening by a single c-EOAE recording attempt would render an unrealistic high number of ears not showing a c-EOAE. So, for the screening purpose of c-EOAE recording in VLBW infants, repeated testing is necessary.

SPECIFICITY AND SENSITIVITY

Healthy newborns

This study *(Chapter 2 to 4)* evaluated the possibility of screening healthy newborns with a c-EOAE recording. For the purpose of screening specificity and sensitivity are important, figures that can only be evaluated using a 'golden standard' audiological test to compare with c-EOAE recording data. At present in newborns the most reliable audiological method is Brainstem Electric Response Audiometry (BERA). Studies that did combine BERA and c-EOAE recording in small numbers of newborns reported a relation between BERA thresholds and the presence or absence of c-EOAEs *(Bonfils et al, 1988a,b; Stevens et al, 1990)*. Specificity and sensitivity figures tend to exceed 90%, which is promising for the purpose of screening.

The specificity of the c-EOAE screen gives the proportion of normal hearing newborn ears that indeed showed a c-EOAE. Since the prevalence of moderate to severe permanent bilateral hearing loss in healthy newborns is below 0.1% we assume that all healthy newborns included in this study were normal hearing and should have shown a c-EOAE. Consequently, we might replace prevalence by specificity of the c-EOAE in this population. Accordingly, the results of this study revealed that the specificity of c-EOAE screening in healthy newborns 2 to 4 days after birth is 95 to 99% *(Chapter 4)*. This means that the number of infants that showed no c-EOAE and should be followed up although they are not hearing impaired (false positives), can be acceptably low for screening purposes. When necessary the number of false positives can be reduced by repeating the c-EOAE recording in ears initially not showing a c-EOAE.

Sensitivity is another important issue of a screening method. In other words how effective is the c-EOAE recording in detecting an ear that is indeed less sensitive to sound than normal. To evaluate this we need a 'golden standard' and a considerable amount of impaired ears. In this study the number of impaired ears expected on statistical grounds has been only 1 to 2, which is to small to determine reliable values for the sensitivity of the c-EOAE-screen.

Concluding, future c-EOAE studies evaluating mass screening should entail combined BERA and c-EOAE recordings. Infants failing to show a c-EOAE as well as a substantial number of infants showing a clear c-EOAE should be examined by BERA. Then reliable values for the specificity and sensitivity of the c-EOAE screen in healthy newborns can be presented. This study infers a c-EOAE specificity in healthy newborns above 95%, which is high enough for screening.

VLBW infants

Infants who are born with a birth weight less than 1500 g are at risk for hearing disability *(Joint Committee on Infant Hearing, 1991)*. The overall prevalence of hearing impairment from mild to severe, uni-/bilateral in this high risk infant population is reported to be 10 to 100 times higher than in the infants not at risk *(Despland and Galambos, 1980; Lary et al, 1985; VanZanten et al, 1988)*. So, preferably this population should be audiologically tested at least in the first few months of life. Since in our hospital, this population cannot be covered for practical reasons using BERA as an audiological method, we studied the c-EOAE recording as a useful test for ear function screening in these infants. Studies in neonatal intensive care (NICU) babies reported a c-EOAE prevalence of about 80 to 90% *(Stevens et al, 1987, 1989; Uziel and Piron, 1991; Webb and Stevens, 1991; Bonfils et al, 1992)*. However, the criteria used to admit an infant to the NICU differed per study. Consequently, these studies probably tested different subgroups of newborns. VLBW infants are a specific subgroup of NICU infants with most of their medical problems resulting from a low birth weight and premature birth. As our hospital is a tertiary referral hospital a negative selection of VLBW infants was probably included in this study. Therefore we described the characteristics of the VLBW infant population extensively *(Chapter 7)*.

As discussed above we need BERA results for the presentation of specificity and sensitivity of c-EOAE recording. So, this cannot be provided by this study. Also in the literature, specificity and sensitivity figures for c-EOAE recording are lacking in this specific infant group and should thus be established in future research by combining c-EOAE and BERA in a larger number of infants.

Since the overall c-EOAE prevalence in VLBW infants after single recording was only 83% in this study, while the expected percentage of normal hearing ears is about 95%, we conclude that the specificity in VLBW infants is not high enough for the purpose of screening. Repeated recordings are necessary.

WHERE AND WHEN TO SCREEN

Healthy newborns

Considering the c-EOAE prevalence we should screen healthy newborns starting 2 to 4 days after birth. In the typical Dutch circumstances however, only about two third of the newborns is born in hospital. The percentage of newborns still in hospital after 4 days is estimated to be less than 10%. This latter figure is probably not very different from other western countries in spite of the fact that a higher percentage of neonates may be born in hospital there. In order to cover the entire (dutch) population of newborns the well baby ward cannot serve as the test site, due to the age dependent c-EOAE prevalence. A different occasion featuring comparable feasibility and c-EOAE prevalence figures will have to be found. As the prevalence of chronic middle ear effusion increases up to 5-7% in the first year of life and the success rate of c-EOAE recording probably decreases we think that the c-EOAE screen should definitely be established before the age of 3 months. In the Netherlands a larger scale study hopefully will soon be started to investigate if an occasion can be realized integrated in our well baby health care system. In other countries (Rhode Island (USA) and Copenhagen County (Denmark)) larger scale screening programs are already in progress.

VLBW infants

Because we experienced great difficulty in making a c-EOAE recording in a VLBW infant we determined the success rate of c-EOAE recording, figures that are usually missing in the reports by other researchers, but very important for possible screening application of the c-EOAE recording. Especially when the infants were tested at a higher age at the outpatient clinic we needed much more time to settle the infant at rest before c-EOAE recording could be started compared to healthy newborns. Even then, the success rate of recording was lower than in healthy newborns. As the success rate of recording and the c-EOAE prevalence in the ward or at the outpatient clinic were counteracting it seems impossible to point out any age of VLBW infants acceptable for screening by c-EOAE. Usually we needed repeated recordings to make one successful c-EOAE recording that also showed a clear c-EOAE in a VLBW infant. Adding up the total time necessary, we estimated that this time consumption is comparable to that necessary to do an BERA test in a considerable proportion of infants. And BERA yields more information, the type and degree of the hearing loss. This leaves us with the same logistic problem, that not the entire VLBW infant population in our hospital can be screened. A single c-EOAE recording attempt as the only possible method of audiological testing of a VLBW infant should best be done between about 40 and 53 weeks postconceptional age, preferably some weeks after discharge from hospital. This can possibly be done if the VLBW infants visit the well baby health care centre, like healthy newborns. Yet, BERA should be done when possible, and especially in those VLBW infants who for some reason do not visit the well baby health care centre.

TECHNICAL ASPECTS OF C-EOAE RECORDING

Test time

A healthy newborn is asleep virtually all day. Generally the infant is only slightly distressed by fitting the probe and sleeps through the c-EOAE recording. Nevertheless, the time period necessary to make a c-EOAE recording in newborns is significantly longer than in adults *(Chapter 4)*, in whom it takes only 1 to 2 minutes. This can be explained by the fact that a newborn cannot be considered as cooperative. This was also mirrored in the less favourable artefact-rejection level and stimulus stability in newborns. The duration of recording in this study was up to 7 minutes for 80% of the ears tested.

The 'Quickscreen' analysis mode of the recent ILO software version has a higher stimulus repetition rate and thus results in a reduction of the test time too. The shorter post-stimulus time window (10 ms) for c-EOAE analysis results in a shorter c-EOAE waveform that contains mainly high frequency emissions.

Thornton *(1993)* proposed a method to extremely reduce the test time to less than 5 s by utilising effective stimulation rates up to 840/s with a pseudo-random click sequence.

However, we always attempted to do a complete recording, i.e. up to 260 stimulus sequences. As c-EOAE level and prevalence are related, the higher newborn response level likely allows for a faster c-EOAE recording in newborns than in adults. The mean measurement time will be significantly shorter in a considerable amount of infant ears if c-EOAE scoring is done already during the recording and recording is stopped as soon as a clear c-EOAE shows up. The savings on measurement time in a mass screening program can be huge.

Scoring method

Either the experience of the examiner or a reliable objective c-EOAE criterion must be used to judge whether a c-EOAE is present in a recorded response or not. In this study the presence of a c-EOAE was identified by visual scoring, but for mass-screening purposes an objective c-EOAE detection criterion is imperative. To evaluate an automated method of scoring, we compared our visual scores with one of the objective variables provided by the ILO88, the c-EOAE reproducibility *(Chapter 4)*. We thus found that with a 'repro'-criterion of 50% no ears pass the objective EOAE screen that failed the subjective visual screen, and only 3.6% of the subjective visual passes failed the objective screen. So, if we consider the infants failing to show a c-EOAE to be hearing impaired, 50% is a safe criterion in the sense that all fails are detected. Considering the infants showing a visually present c-EOAE as not to be hearing impaired, the false alarm rate using a 50% 'repro'-criterion is 3.6%. Automatic c-EOAE scoring by using the 'repro' might be refined by filtering and/or windowing the response and result in an even lower false alarm rate. Yet, there may well be a better objective variable than the 'repro' to automate the scoring of c-EOAEs. Preliminary pure-tone audiogram and c-EOAE recording data acquired in adults in our clinic revealed that the weighted response level (WRL), defined as the product of c-EOAE response reproducibility and level, is a reliable objective figure. This was confirmed in children by Welzl-Müller *(1994)*. In newborns the WRL still needs to be evaluated as a automatic c-EOAE score. Of course the results of any automatic c-EOAE scoring method to be used in newborns will have to be related to the specificity and sensitivity of combined c-EOAE and BERA mass-screening to review the true value of the automatic c-EOAE score.

CONCLUSIONS

1- The c-EOAE level in healthy newborns was demonstrated to grow in the first days post partum. The time period of growth differs per individual ear, but predominantly occurs from day 0 to day 2 after birth. We think this is due to the fact that the middle ear has to be cleared from amniotic fluid.

   As the c-EOAE level and c-EOAE prevalence are related we observed an increase in c-EOAE prevalence to 99% in ears of infants older than 108 h. To minimize the number of false positives in a c-EOAE mass-screening program, newborns should not be screened before 2 to 4 days post partum.

2- This study detected SOAEs in 78% of the healthy newborn ears tested. This percentage however is dependent on the noise floor and other characteristics of the equipment. We suggest to present SOAE prevalence figures relative to an absolute reference level. Thus we found that about 50% of the newborn ears show SOAEs stronger than 10 dBSPL. The SOAE prevalence relative to a reference level of 20 dBSPL is 20%, while such strong SOAE are very rare in adults. The SOAE prevalence, the number of SOAEs per ear and the SOAE frequencies are significantly higher than in adults. Like in adults, SOAEs in newborns tend to be more prevalent in the right ear and in females.

3- SOAE presence and a higher c-EOAE level are shown to be related. The major part of the difference in c-EOAE level strength between healthy newborns and adults is explained by the stronger SOAE presence in newborns.

4- Our data do not allow to distinguish whether changes in OAE features with age, like the level and frequency content, are influenced by middle or inner ear development. Future research might shed light on how the maturation of separate elements of the ear accounts for the developmental changes in OAE characteristics from premature birth into adulthood.

5- Given the success rate of making a recording and the c-EOAE prevalence, screening of healthy newborns in the well baby ward a few days after birth is feasible. In order to study the possibility to screen the entire newborn population (in the Netherlands), the feasibility should be re-evaluated at a larger scale and at a different test site. When the results appear to be promising, specificity and sensitivity figures of c-EOAE recording in healthy newborns should be acquired by brainstem electric response audiometry of a large number of infants showing a clear c-EOAE as well as all infants who do not.

6- In VLBW infants it is difficult to recommend an optimal age for c-EOAE recording, because the success rate of recording and the c-EOAE prevalence are counteracting. The best age to attempt c-EOAE recording probably is between 40 and 53 weeks postconceptional age.

Until about 40 weeks postconceptional age the individual variation in c-EOAE level is large, probably due to transient middle ear dysfunction. Yet, as a reflection of maturation of the ear, a mean growth in c-EOAE level with age was found.

7- The method of c-EOAE recording promises to be a viable tool for screening on ear dysfunctions. The use of a reliable objective detection criterion is possible. There are some technical options for even further reduction of measurement time per infant.

SAMENVATTING EN CONCLUSIE

HET VERSCHIJNSEL OTO-ACOUSTISCHE EMISSIE

De klik-gestimuleerde oto-acoustische emissie (c-EOAE) is een geluid aanwezig in de gehoorgang na stimulatie van het oor met een klik. De c-EOAE bleek niet te registreren na klik stimulatie van een kunstoor *(Hoofdstuk 1, figuur 2)*. Het oor van de mens bestaat uit een uitwendig gedeelte, de oorschelp en de gehoorgang, het middenoor met het trommelvlies en de gehoorbeenketen en het binnenoor, het feitelijke gehoorzintuig. Geluid moet dus door de gehoorgang en het middenoor om bij het binnenoor aan te komen. Het middenoor was onwaarschijnlijk als oorsprong van de c-EOAE. Het middenoor is namelijk goed gedempt en het is dan ook onwaarschijnlijk dat de c-EOAE, die geregistreerd kan worden nadat de klik-stimulus al uitgedooft is, hieruit afkomstig zou zijn. Eigenlijk zijn er nogal wat aanwijzingen dat de c-EOAE gegenereerd wordt in het slakkehuis, het binnenoor. Dit geluid uit het oor werd voor het eerst waargenomen door Kemp in 1978.

De c-EOAE is een zeer zwak geluid dat geregistreerd kan worden met een zgn. probe, die in de gehoorgang moet worden gepositioneerd, zodat het oor afgesloten wordt *(Hoofdstuk 1, figuur 1)*. In de probe zit een telefoontje waar de klik stimulus uitkomt. Bovendien bevindt zich in de probe een microfoontje, dat de geluiden in de gehoorgang opvangt. De probe is verbonden met een computer om de opgevangen geluiden te verwerken. Omdat de c-EOAE zo'n zwak geluid is, is het niet eenvoudig de c-EOAE te onderscheiden van achtergrond ruis: ander geluid in de gehoorgang, zoals ademgeluid, hartslag, etc. Met de huidige apparatuur wordt dat onderscheid gemaakt door de stimulus heel vaak aan te bieden (ca. 1000 maal) en de computer uit te laten rekenen welk geluid opgevangen na één stimulus steeds hetzelfde is als na de vorige stimulus. De c-EOAE is een reactie op de stimulus en de golfvorm van het geluid is daarom steeds dezelfde na elke stimulus, terwijl de golfvorm van het achtergrond geluid voortdurend verandert.

Enkele jaren na de ontdekking van c-EOAEs werden er zonder enige stimulatie van het oor met geluid nog andere geluiden, bijna zuivere tonen, in de gehoorgang geregistreerd. Dit zijn spontane oto-acoustische emissies (SOAEs). Aangezien SOAEs beïnvloed (gesynchroniseerd) kunnen worden door een klik stimulus kunnen ze waarneembaar zijn in de c-EOAE registratie.

Er werden nog andere typen EOAEs gevonden, die uiteraard door andere stimuli dan de klik gegenereerd worden. Om deze EOAEs te registreren is ook een andere manier van signaal verwerking vereist. De c-EOAE registratie is daarbij vergeleken relatief eenvoudig.

OAEs EN SLECHTHORENDHEID

Het is onbekend hoe OAEs nu precies worden gegenereerd, maar het is waarschijnlijk dat ze ontstaan als nevenverschijnsel bij actieve processen in het binnenoor, samenhangend met het normale horen *(Hoofdstuk 1).* Met z'n karakteristieke vorm kan de c-EOAE golfvorm getypeerd worden als de 'handtekening van het oor', die per oor verschilt en na lange tijd nog dezelfde is. Ook de SOAE frequenties blijven in de loop der jaren constant.
In het algemeen kunnen we stellen dat OAEs stabiel zijn mits de functie van het binnenoor niet verandert. Wanneer specifiek het binnenoor beschadigd wordt door bepaalde factoren, veroorzaakt dit het verdwijnen van het OAE fenomeen. OAEs zijn dan ook afwezig in oren met een matig tot ernstig gehoorverlies op basis van afwijkingen in het binnenoor. Deze en andere bevindingen ondersteunen de gedachte dat OAEs van het binnenoor afkomstig zijn. Kennelijk 'lekken' er geluidstrillingen uit het binnenoor in de gehoorgang eventueel spontaan en/of na stimulatie van het oor met geluid.

We kunnen OAEs beschouwen als objectief meetbare geluiden die uniek zijn voor het gezonde binnenoor en dit biedt klinisch perspectief *(Hoofdstuk 1).* De c-EOAE is aanwezig in 90 tot 100% van de oren van normaal horende volwassenen en afwezig in oren met een binnenoor gehoorverlies boven de 15 tot 40 decibel (dB). Zodoende kunnen we de c-EOAE registratie gebruiken om te screenen op een (sub)normaal gehoor. SOAEs zijn minder specifiek, aangezien ze slechts in 30% van de oren van normaal horende volwassenen voorkomen. Over het algemeen zijn ze afwezig in oren met een binnenoor slechthorendheid van 25 dB of meer.
Bij de registratie van OAEs is het wel erg belangrijk dat de functie van het middenoor normaal is, omdat daar doorheen de voortgeleiding van de stimulus en met name ook van de OAE mogelijk moet zijn. Een slechte functie van het middenoor, b.v. door vocht achter het trommelvlies resulteert in een verzwakken van de OAE, vaak zoveel dat de OAE onmeetbaar 'zwak' wordt.
Er bestaan ook vormen van slechthorendheid die veroorzaakt worden door afwijkingen 'achter' het binnenoor, nl. ergens op de weg die de geluidsinformatie aflegt tussen het binnenoor en de hersenen. In een oor met een dergelijke 'retrocochleaire' afwijking, die zelfs tot doofheid kan leiden kunnen we soms toch nog een OAE vinden. We tonen met de OAE namelijk alleen een normale functie van het oor zelf aan.

C-EOAEs EN OORSCREENING BIJ PASGEBORENEN

Het voorkomen van matig tot ernstig gehoorverlies bij gezonde pasgeborenen bedraagt 1 tot 2 per 1000. Momenteel worden kinderen in Nederland pas op de leeftijd van 9 tot 12 maanden audiologisch onderzocht. Een geschikte methode om het gehoor al in de eerste

levensmaanden te screenen ontbreekt nog. De standaard test methode voor pasgeborenen, hersenstam audiometrie, is te duur voor screening.
In het Sophia Kinderziekenhuis Rotterdam lukt het zelfs niet om alle pasgeborenen, die een verhoogd risico op slechthorendheid hebben te testen met het hersenstam gehooronderzoek, dat zeer tijdrovend is.
De c-EOAE registratie is mogelijk bruikbaar voor het screenen van de oorfunctie in beide populaties van pasgeborenen. Dit kan van groot belang zijn voor het vervroegen van de diagnose en starten van revalidatie bij kinderen met een matig tot ernstig aangeboren binnenoor gehoorverlies. Onderzoeken, die voorafgaand aan deze studie in kleinere aantallen kinderen en met laboratorium apparatuur zijn uitgevoerd, lieten veelbelovende resultaten zien.

DOELEN VAN DEZE STUDIE

Om de mogelijkheid van oorscreening met behulp van de c-EOAE registratie te evalueren werden allerlei aspecten van deze test bestudeerd na metingen in meer dan 1000 oren van gezonde pasgeborenen, kort na de geboorte en met commerciële apparatuur. In een populatie van kinderen met een zeer laag geboorte gewicht (VLBW), die een verhoogd risico op slechthorendheid hebben, werden zowel de aspecten van screening door middel van de c-EOAE registratie bestudeerd als ook de mogelijke veranderingen in c-EOAE eigenschappen met de leeftijd. Deze kinderen werden daarom meerdere malen onderzocht.

GEZONDE PASGEBORENEN

Kort na aanvang van de studie in ongeveer 1000 oren van gezonde pasgeborenen bleek dat de sterkte van de c-EOAE toenam in de eerste dagen na de geboorte *(Hoofdstuk 2)*. Aangezien de detectie van een c-EOAE in de response afhankelijk is van de sterkte van de c-EOAE was dit een belangrijke bevinding met het oog op screening. Bij een uitgebreidere bestudering van de groei in c-EOAE sterkte vonden we dat de toename in c-EOAE sterkte fors verschilde per oor *(Hoofdstuk 4)*. In de meeste oren vond de groei voor het grootste gedeelte plaats van dag 0 tot dag 2 na de geboorte. De periode van groei toonde geen relatie met de uiteindelijke sterkte. Naar onze mening is de groei gerelateerd aan de periode na de geboorte waarin het middenoor geklaard moet worden van vruchtwater.

SOAEs waren zeer frequent aanwezig in oren van pasgeborenen *(Hoofdstuk 5)*. We vonden in 78% van 176 opeenvolgende oren SOAEs, hetgeen significant hoger is dan de 30% die in oren van volwassenen gerapporteerd wordt. Deze percentages worden echter mede bepaald door de sterkte van het achtergrond lawaai waar de SOAE boven uit moet steken om gedetecteerd te worden. Het lijkt ons daarom beter om het voorkomen van SOAEs uit te drukken ten opzichte van een absolute referentie sterkte. Dan vonden we een voorkomen van

SOAEs sterker dan 20 dBSPL in 20% van de pasgeborenen oren, terwijl deze sterke SOAEs zelden voorkomen bij volwassenen.

Bij gezonde pasgeborenen varieerde de sterkte van de c-EOAE tussen 1.6 en 38.6 dBSPL (gemiddeld 20.2 dBSPL), hetgeen significant sterker is dan wij en andere onderzoekers vonden in oren van normaal horende volwassenen (2.7 tot 20.6 dBSPL; gem. 12.8 dBSPL). Bray en Kemp *(1987)* suggereerden dat dit verschil in c-EOAE sterkte verklaard kan worden doordat het volume van de gehoorgang bij pasgeborenen kleiner is en daardoor de geluidsdruk relatief groter. Ons onderzoek toonde echter aan dat de sterkere c-EOAEs vooral het gevolg zijn van het frequente voorkomen van sterke SOAEs bij pasgeborenen *(Hoofdstuk 5)*.

Het spectrum van de c-EOAE van pasgeborenen bevat vooral hoge frequenties. 70% van de SOAE frequenties is ook hoog (groter dan 2 kHz) *(Hoofdstuk 3 en 5)*. Dit is in tegenstelling met de bevindingen bij volwassenen, die voornamelijk laag frequente OAEs vertonen (1 tot 2 kHz). Toekomstige studies zullen moeten aantonen in hoeverre verschillen in de voortgeleiding van geluid door het middenoor of verschillen in eigenschappen van het slakkehuis tussen pasgeborenen en volwassenen de veranderingen in frequentie samenstelling kunnen verklaren.

De c-EOAE registratie kon in 96% van de oren van gezonde pasgeborenen goed worden uitgevoerd *(Hoofdstuk 3)*. Net als de sterkte van de c-EOAE, stijgt het percentage van geïdentificeerde c-EOAEs in de registraties in de eerste dagen na de geboorte. Bij pasgeborenen van enige dagen oud blijkt de meting op zich vaak goed uit te voeren en met screening als doel vertonen genoeg oren een c-EOAE. Om de werkelijke waarde van de c-EOAE meting te bepalen zal in de toekomst in een groot aantal oren dat een c-EOAE vertoont met een andere gehoortest gecontroleerd moeten worden of er inderdaad een normale gevoeligheid voor geluid bestaat. Verder moet er een groot aantal oren van pasgeborenen met een verminderde gevoeligheid voor geluid getest worden om te controleren of die dan géén c-EOAE vertonen.
Om screening d.m.v. c-EOAE metingen tot een succes te maken zouden pasgeborenen pas na enkele dagen onderzocht mogen worden *(Hoofdstuk 2 t/m 4)*. Aangezien in Nederland net als in de landen om ons heen de meeste gezonde pasgeborenen na enkele dagen niet (meer) in het ziekenhuis zijn moet naar een andere locatie gezocht worden. Om de meting goed uit te kunnen voeren moeten pasgeborenen waarschijnlijk voor de leeftijd van 3 maanden onderzocht worden. Hopelijk zal in Nederland binnenkort een onderzoek starten om te evalueren of het mogelijk is de c-EOAE screening op het consultatiebureau te doen.

KINDEREN MET EEN ZEER LAAG GEBOORTE GEWICHT (VLBW)

144 VLBW kinderen werden in het onderzoek ingesloten *(Hoofdstuk 6 en 7)*. Tijdens de metingen waren ze tussen de 29 en 66 weken oud, gerekend vanaf de conceptie.

De sterkte van de c-EOAE bij VLBW kinderen was significant lager dan bij gezonde pasgeborenen *(Hoofdstuk 6)*. Vanaf ongeveer 40 weken postconceptie (normaal gesproken het moment van geboorte) benaderde de sterkte van de c-EOAEs die van gezonde pasgeborenen. Gemiddeld werd er een groei in de sterkte van de c-EOAE met de leeftijd gevonden, maar in het individuele oor van VLBW kinderen varieerde de sterkte nogal met de leeftijd. Wij denken dat deze variatie in sterkte veroorzaakt wordt door variaties in de functie van het middenoor. Het is bekend dat het middenoor bij relatief veel VLBW kinderen (intermitterend) slecht functioneert, zeker wanneer ze, zoals veel van deze kinderen, lang beademd zijn geweest. Helaas hebben we de functie van het middenoor in deze studie niet kunnen testen. Toekomstig onderzoek zal mogelijk kunnen uitwijzen of de gemiddelde groei van de c-EOAE sterkte het gevolg is van ontwikkeling van het middenoor en/of het binnenoor.

De c-EOAE meting is bij VLBW kinderen veel moeilijker gebleken dan bij gezonde pasgeborenen *(Hoofdstuk 6)*. Waarschijnlijk hebben zowel de lawaaierige omgeving waarin de VLBW kinderen veelal onderzocht werden (pasgeborenen 'high care' en polikliniek pasgeborenen), als de onrust van deze kinderen zelf hiertoe bijgedragen. Het was duidelijk makkelijker om de kinderen op jonge leeftijd op de high care te meten dan op de polikliniek, wanneer de kinderen tevens ouder waren. Echter het aantal registraties dat een c-EOAE vertoonde was lager wanneer de meting op de high care gedaan was dan op de polikliniek. Op de high care kon een oor ook het ene moment een c-EOAE vertonen en een week later niet meer. Dit kan mogelijk weer verklaard worden door de variatie in functie van het middenoor. Kortom, vaak zullen meerdere pogingen/metingen noodzakelijk zijn om bij een VLBW kind een c-EOAE te vinden. Waarschijnlijk is het bij deze VLBW kinderen dan ook beter om een zgn. 'brainstem' gehooronderzoek te doen.

CONCLUSIE

De c-EOAE is een geluid <u>uit</u> het oor dat bijna in alle normale oren aanwezig is. Bij pasgeborenen is de c-EOAE al vrij snel na de geboorte aanwezig. Toch moet, als de c-EOAE toegepast zou gaan worden voor oorscreening bij pasgeborenen niet te vroeg na de geboorte gescreend worden. Omdat de sterkte van de c-EOAE de eerste dagen na de geboorte nog toe neemt zouden direct na de geboorte onnodig veel oren zonder c-EOAE gevonden worden. SOAEs, geluiden uit het oor zonder stimulatie van het oor, komen frequenter voor en zijn ook sterker bij pasgeborenen dan bij volwassenen. De aanwezigheid van SOAEs in een oor blijkt te resulteren in een sterkere c-EOAE.

Oorscreening met de c-EOAE registratie bleek mogelijk op de kraamafdeling bij pasgeborenen van enkele dagen oud, maar om bij "alle" pasgeborenen een goed c-EOAE onderzoek uit te kunnen voeren moet gezocht worden naar een andere locatie dan de kraamafdeling. Oorscreening met de c-EOAE meting is niet aan te raden bij VLBW kinderen. Zowel op de high care afdeling als op de polikliniek moest ongeveer één derde van de kinderen opnieuw gemeten worden, óf omdat de meting niet lukte, of omdat geen c-EOAE gevonden werd. Weliswaar zou na herhaaldelijk meten bij 95% van de gevallen een c-EOAE gevonden worden, maar zo'n procedure is erg tijdrovend en daarom minder geschikt.

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Renée Kok

Curriculum Vitae

Margaretha Renée Kok werd op 18 januari 1964 geboren in Amsterdam. In 1982 behaalde zij haar VWO diploma aan het Koningin Wilhelmina Lyceum in Oostburg. Hierna is zij geneeskunde gaan studeren aan de Erasmus Universiteit Rotterdam. In mei 1989 werd het artsexamen behaald. In deze periode maakte zij kennis met wetenschappelijk onderzoek in de Audiologie. Dit leidde in januari 1990 tot haar aanstelling als wetenschappelijk medewerkster op de afdeling Keel- Neus- en Oorheelkunde van de Erasmus Universiteit, en uiteindelijk tot dit proefschrift. Vanaf augustus 1992 tot februari 1994 is zij tevens part-time werkzaam geweest als arts-assistente Algemene Heelkunde in het Merwede Ziekenhuis Dordrecht. Sinds april 1994 is zij arts-assistente op de afdeling Keel-, Neus- en Oorheelkunde van het Dijkzigt Ziekenhuis Rotterdam.