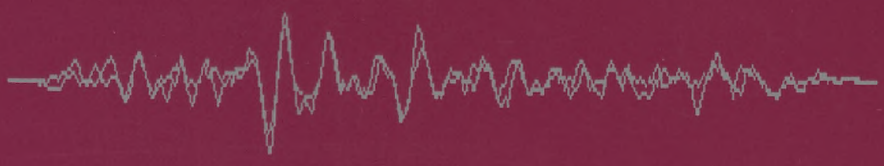
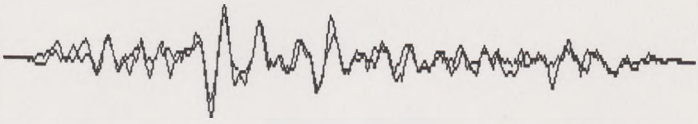
CLICK EVOKED
OTOACOUSTIC EMISSIONS
IN CLINICAL PRACTICE



C.C. Tilanus

CLICK EVOKED
OTOACOUSTIC EMISSIONS
IN CLINICAL PRACTICE



Click evoked OtoAcoustic Emissions in clinical practice

(with a summary in English)

Door kliks opgewekte OtoAkoestische Emissies in de klinische praktijk

(met een samenvatting in het Nederlands)

Proefschrift

ter verkrijging van de graad van doctor aan de Universiteit Utrecht
op gezag van de Rector Magnificus, Prof. Dr J. A. van Ginkel,
ingevolge het besluit van het College van Decanen
in het openbaar te verdedigen op
dinsdag 2 april 1996 des namiddags te 16.15 uur

door

Constantijn Cyril Tilanus
geboren op 2 april 1961 te Amsterdam

Promotores: Prof. Dr E.H. Huizing, *Universiteit Utrecht*
Prof. Dr Ir H.P. Wit, *Rijksuniversiteit Groningen*

CIP-DATA KONINKLIJKE BIBLIOTHEEK, DEN HAAG

Tilanus, Constantijn Cyril

Click evoked otoacoustic emissions in clinical practice /
Constantijn Cyril Tilanus. - [S.l. : s.n.]. - ill., fig.
Thesis Universiteit Utrecht. - With ref. - With summary
in Dutch.
ISBN 90-9009282-X
Subject headings: hearing / audiology / otoacoustic emissions.

Stellingen behorend bij het proefschrift:

Click evoked otoacoustic emissions in clinical practice

C.C. Tilanus

1 Stellingen bij een proefschrift vormen de pijlers van de brug tussen wetenschap en maatschappij.

2 Bij groepen normaalhorenden bestaat een verband tussen otoakoestische emissiesterkte en gemiddelde gehoordrempel.

3 Er is geen klinisch relevant effect van veroudering op de sterkte van otoakoestische emissies.

4 Het feit dat direct na buisjesplaatsing wegens OME bij kinderen weinig otoakoestische emissies worden gevonden, kan wijzen op een tijdelijke lawaaidip ten gevolge van de ingreep.
(Ann Otol Rhinol Laryngol (1995) 104:297-300)

5 De polariteitsomkering van de cochleaire sommatiepotentiaal bij cavia's onder invloed van anoxie duidt erop dat deze potentiaal uit verschillende componenten bestaat. *(Eur Arch Otorhinolaryngol (1992) 249:12-15)*

6 Het ziektebeeld van de chronisch recidiverende polychondritis toont het primaat van klinische blik en nauwkeurige anamnese boven geavanceerde laboratoriumdiagnostiek voor zeldzame diagnosen.
(Ned Tijdschr Geneesk 1994 (138):1963-66)

7 Radiotherapie voor de behandeling van maligne tumoren heeft een in wezen homeotherapeutische grondslag, daar vele van deze tumoren door soortgelijke straling geïnduceerd kunnen worden.

8 De verschuiving van klinische naar ambulante zorg heeft tot gevolg dat de capaciteit van Nederlandse ziekenhuizen niet zozeer bepaald wordt door het aantal bedden, maar door het aantal beschikbare parkeerplaatsen.

9 De abominabele kwaliteit van veel omroepberichten in de trein heeft één voordeel: reizigers kunnen zich gemakkelijker inleven in de dagelijkse problemen die slechthorenden ondervinden.

10 Het diagnostisch en therapeutisch belang van stilte kan moeilijk overschat worden.

11 Lingua quasi docta medicorum quae vulgo 'potjeslatijn' dicitur, vere praecipue graecam non latinam originem habet.
(Artsenjargon, in de volksmond potjeslatijn, blijkt qua oorsprong vooral Grieks te zijn)

12 Het is hoog tijd dat de Nederlandse Gebarentaal als officiële taal erkend wordt.

13 De implementatie van een geïntegreerd systeem van in eerste aanleg op zowel strategisch, tactisch als operationeel niveau gerichte efficiëntiebevorderende maatregelen teneinde tot een duurzame doelmatigheidsgerichte en toetsbare organisatiestructuur te komen, kan vaak als autoreflectief signaal van onvoldoende intrinsieke transparantie worden geïnterpreteerd. Met andere woorden: kwaliteitsbeleid is een ernstig symptoom van bureaucratitis.

14 Ongebreidelde protocollering leidt tot hamburgergeneeskunde.

15 Technologische vooruitgang gaat gepaard met schijnbaar tegenstrijdige ontwikkelingen, zoals onder andere blijkt uit de computer, die van rekentuig tot taalmachine (tekstverwerker) werd; de radio, die vanuit de ether vastgekabeld werd; en de telefoon, die juist het snoer ontgroeide tot een draadloos fenomeen. Evenzo zal waarschijnlijk binnen enige decennia de automobiel zijn oorspronkelijk zeer beweegbare karakter geheel verliezen en zich ontwikkelen tot een vaststaande privécabine in het Geïntegreerde Mondiale Filenet (GMF), waarin de gebruiker rustig aan zijn laptop kan werken of draadloos kan bellen met andere Filenetgebruikers.

16 Een promotie is als het rijden van de Elfstedentocht: het kost jaren van voorbereiding, is in één dag voorbij, maar geeft levenslang een goed gevoel.

non scholae sed vitae discimus

voor Geertruid,
Clara, Diede en Ottolien

CONTENTS

List of abbreviations

ABR	Auditory Brainstem Response
CEOAE	Click Evoked OtoAcoustic Emission
DPOAE	Distortion Product OtoAcoustic Emission
EOAE	Evoked OtoAcoustic Emission
HL	Hearing Level
IHC	Inner Hair Cell
MFA	Mid Frequency Average (0.5, 1, 2, 4 kHz)
OAE	OtoAcoustic Emission
OHC	Outer Hair Cell
PTA	Pure Tone Audiogram
SFOAE	Stimulus Frequency OtoAcoustic Emission
SL	Sensation Level
SNHL	SensoriNeural Hearing Loss
SOAE	Spontaneous OtoAcoustic Emission
SPL	Sound Pressure Level
TEOAE	Transient Evoked OtoAoustic Emission

References are listed at the end of each chapter

▸ 1 GENERAL INTRODUCTION

1.1 The assessment of hearing

We are living in an age of communication: interpreting both visual and auditory information is an essential aspect of our lives and links us together to form a society. Listening and speaking are among the most often performed activities and of prime importance to humanity.

In order to receive auditory information adequately, good hearing is therefore essential. Likewise, the assessment of a possible diminution of hearing acuity is important. The sound which we normally recognize as speech is in fact a composition of many tones of different frequencies and intensities. In order to assess the hearing ability of the ear either the complete speech signal or separate tones may be used as stimuli (other specific tests fall beyond the scope of this review). The latter method gives more precise information about the inner ear (cochlea), as it involves less central processing (nerves and brain).

In short, the procedure is as follows: the subject (patient) is offered a test tone produced by a tone-generator, of a certain frequency and intensity in one ear, and asked if he hears the sound or not. If he does hear it, the sound is made weaker and weaker (i.e. the intensity is diminished) until he no longer perceives the tone. The lowest audible intensity is then called the pure tone threshold for that specific frequency. The procedure is continued with other test frequencies, until a complete set of thresholds is recorded. Usually, this comprises the thresholds for octave tones from 125 to 8000 Hz, sometimes supplemented with tones of 1500, 3000 and 6000 Hz. The graphic representation of the set is called an audiogram, because it describes the hearing of the subject's ear. The audiogram may be taken from one or both ears with a headset, bone conductor or 'free field' stimulation, respectively.

The hearing thresholds are expressed in decibels hearing level (dB HL), which is a relative measure comparing the sound pressures (thresholds) to a standard (e.g. ISO 1964) obtained from a large group of normal hearing ears. A threshold of 0 dB HL means the hearing is normal, a threshold of 10 dB HL means the sound intensity of the tone must be 10 times greater to be heard, a threshold of 20 dB HL means the sound intensity must be 10 x 10 = 100 times greater to be heard, etc. If a person has very good hearing, his pure tone threshold for a certain frequency may be as low as -10 dB HL, whereas in a case of very poor hearing (deafness), thresholds of 100 to 120 dB HL are not uncommon. Audiometry in this way is straightforward and has been performed

and standardized as such for many years (e.g. Fowler 1949).

But with the refinement of the audiometric techniques and further development of the technical possibilities in the first half of this century, some very interesting features emerged, which led to the development of new concepts on hearing and finally to the discovery of otoacoustic emissions: (a) the ear seems to be very highly tuned, which means that it has an incredible frequency selectivity. For example, tones with frequencies of 1000 and 1002 Hz may be well distinguished from each other, although their vibration cycles differ only by two millionth of a second. Furthermore, (b) the ear possesses an enormous dynamic range: the difference in intensity between tones from the 'top' and the 'bottom' of the audiogram (which can all be heard with the same ear) is of the order of 1 to 10^{14}. In comparison, if the ear were a scale, both mosquito and whale could be accurately weighed by it. (c) Another highly interesting feature is the so-called microstructure of the audiogram (Elliott 1958): the thresholds for tones with adjacent frequencies vary by as much as 5 to 15 dB, giving a jagged appearance to the, in this way minutely recorded, audiogram. This varying difference in sensitivity of the ear is 'smoothed out' when louder tones are applied and the subjective loudness of these is measured (Kemp and Martin 1976). Thus, it is a phenomenon which concerns soft tones only. (d) In some normal hearing ears, stimulation with moderate intensity pure tones may lead to a sensation of 'beating' between the stimulus tone and a subjectively experienced ringing tone (the "idiotone") at certain frequencies, coinciding with a localized hearing loss. This is called the "idiophonic effect" (Flottorp 1953, Ward 1955, Wegel 1931). Thus, close examination of the function of the ear revealed aspects which required an adaptation of classical theories on hearing.

1.2 The 'active' ear

The explanation for these phenomena is difficult to give if the ear is considered to be a passive transducer of sound energy, simply changing air vibrations into fluid vibrations, which in turn are converted into nervous impulses (Helmholtz 1863, Békésy 1939). In fact, in 1948 the physicist Gold proposed a theory from a radically different point of view (Gold 1948): what if the cochlea contained actively vibrating elements which amplified the incoming sound, comparable to the amplifiers found in radio equipment? This would not only explain the high

frequency selectivity and sensitivity of the ear, but it could also provide insight into the other phenomena mentioned above. As a consequence, he predicted, even without external stimulation, some mechanical energy might be radiated out from these active elements in the ear, which should be measurable in the ear canal with a sensitive instrument. In this way, information about the functioning of the ear could be obtained in a very direct manner, completely different from the audiogram.

It took another thirty years for Gold's hypothesis to be proven. Finally, in 1978, Kemp published a paper titled "Stimulated acoustic emissions from within the human auditory system" (Kemp 1978), in which he described his findings in normal ears and ears with hearing loss of cochlear origin. As predicted, there appeared to be an acoustic response of the healthy ear to low intensity stimuli, which was measured using a signal averaging technique (to improve the signal to noise ratio).

The soft tones which Kemp elicited in normal cochleae by clicks were also found to occur spontaneously (Wilson 1979, Kemp 1981), though not in all ears. The phenomenon of the (stimulated) acoustic re-emission was originally termed "evoked cochlear mechanical response" (Kemp 1979b) or "Kemp echo" (Wilson 1979, Wit et al 1981), but gradually became known as "stimulated acoustic emission" or "otoacoustic emission" (Wit and Ritsma 1979, Wilson 1980, Kemp and Chum 1980, Zwicker 1983).

With the actual discovery of otoacoustic emissions (OAEs), two exciting fields for further research came into sight. In an experimental setting, the cochlear mechanics underlying the process of sound transduction and perception could be studied in a non-invasive way *in vivo*. In a clinical setting, measurement of OAEs could be a valuable test of hearing acuity for screening and other purposes (Kemp 1978).

We will first give an overview of the current ideas on the physiological background of OAEs. Next, we will describe their different manifestations, the way they are classified and the available systems for measurement. Then we will elaborate on the actual subject of this study, which concerns the practical application of otoacoustic emissions in assessing hearing thresholds in clinical practice, as compared to the audiogram as 'golden standard'. Evidently, this is only a small portion of all the applications worth investigating.

1.3 Physiological background to otoacoustic emissions

Trying to describe the mechano-electrical transduction process, most authors (e.g. Kemp 1979b, Hudspeth 1989, Norton 1992) agree on the first part: incoming sound is transmitted from the external ear canal via the middle ear (tympanic membrane and ossicles) to the inner ear, more specifically to the fluid of scala vestibuli (perilymph). This causes a vibratory motion of the basilar membrane (BM), which is located between scala media and scala tympani (see Figure 1.1). The basilar membrane supports rows of inner and outer hair cells, which are essential to transduce the mechanical energy into electrical energy that may in turn cause excitation of the nerve endings of the eighth cranial nerve (action potentials).

The apices of the inner and outer hair cells are sealed by tight junctions into the reticular lamina, which runs parallel to the tectorial membrane. The 'hairs' (stereocilia) on the inner and outer hair cells emerge from this layer, which forms a barrier between endolymph (scala media) and perilymph (scalae tympani et vestibuli). The stereocilia are special cell organelles consisting of interlinked rods which may be bent by the overlying tectorial membrane, thus opening and closing ion channels that are thought to be responsible for the variations in generator potentials (Lim 1986).

The second part of the sound transduction processes in the cochlea, in the organ of Corti itself, is more speculative and controversial. A comprehensive review of both anatomic and physiologic aspects is found in Dallos (1992). It is known from experimental studies (Brownell 1983, Brownell et al 1985, Zenner et al 1985) that isolated outer hair cells can contract and relax under the influence of various chemical, electrical and acoustic stimuli, and that they contain actin filaments (Flock and Cheung 1977). It is therefore not unlogical to suppose (e.g. Kemp 1986, Hudspeth 1989) that the passive motion of the basilar membrane, created by the vibration of the perilymph, is enhanced by active contraction of the outer hair cells. They could then be considered the actively vibrating elements that were postulated by Gold.

However, there is only indirect evidence for this hypothesis: the basilar membrane motion as measured by Sellick et al (1982) shows a nonlinear behaviour which could be explained by amplification of small vibrations (soft sounds) by the outer hair cells. This mechanism would explain the mechanical nonlinearity reported by Kemp (1979a). Presumably, the OHC motile response

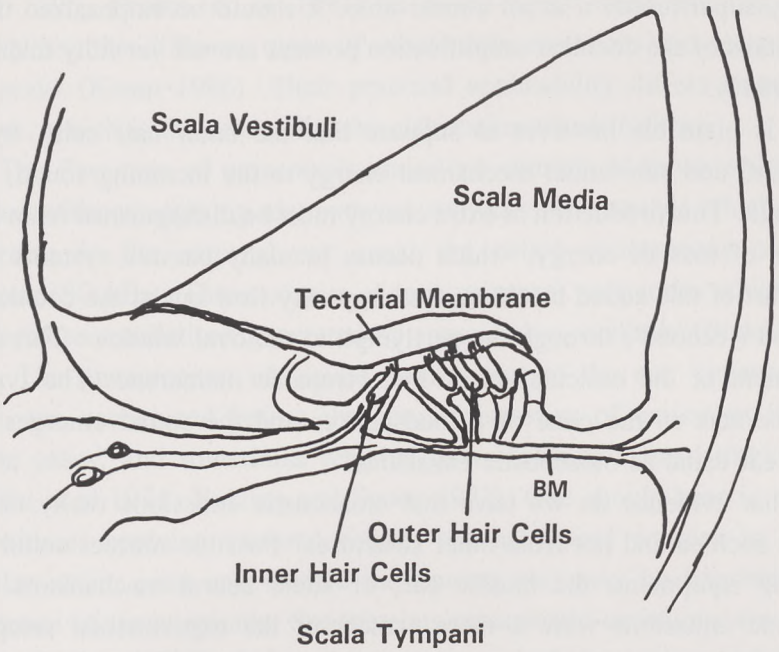


Figure 1.1
Schematic representation of the organ of Corti in the inner ear. The Basilar Membrane is indicated by BM. The outer hair cells are thought to be the site of generation of otoacoustic emissions.

alters the relationship between tectorial membrane and reticular lamina, and thereby modifies the input to IHCs. This contraction and relaxation of outer hair cells can be influenced by efferent nerve endings (Siegel and Kim, 1982), which are found mainly around their bases (e.g. Spoendlin 1986), especially in the basal turns of the cochlea (high frequency regions).

The inner hair cells on the other hand, are much richer in their afferent innervation and seem to be the actual neural (passive) receptors (Lim 1986). There are many other differences between inner and outer hair cells, which we cannot deal with extensively here. Important is that the stereocilia of the inner hair cells do not seem to be in contact with the tectorial membrane, unless (a) the outer hair cells amplify a small incoming vibration, or (b) the sound in itself is so loud that the amplitude of the vibration in the cochlea ('travelling wave') causes them to 'bounce' against the tectorial membrane. In this case the amplification of the basilar membrane motion by the outer hair cells is

obviously superfluous, if at all conceivable. It should be emphasized that the actual details of the cochlear amplification process are not yet fully understood (Dallos 1992).

It is plausible however to suppose that the outer hair cells, by their contraction, add substantial mechanical energy to the incoming sound, if it is soft enough. This production of extra energy must be distinguished from a mere reduction of loss of energy, which occurs in many passive systems (Kemp 1986). Part of this added mechanical energy may flow out of the cochlea: it is rebounced ('echoed') through the perilymph to the oval window. This creates a movement of the ossicular chain and tympanic membrane. The tympanic membrane acts as the cone of a loudspeaker and the sound emerges in the external ear canal as otoacoustic emissions.

What evidence do we have that otoacoustic emissions really originate from the cochlea and not from other structures? Possible sources could be the measuring equipment, the middle ear, or some neural mechanisms. If the otoacoustic emissions were a mere artifact of the experimental setup, they would also be measurable in an artificial ear (e.g. a 2 ml coupler), which is not the case (Kemp 1978). The middle ear cannot be the source of otoacoustic emissions, as its ringing time, which does not exceed 4 ms, is much shorter than the post-stimulus period in which otoacoustic emissions may be detected (from 5 to over 30 ms, Kemp 1978). A neural origin of otoacoustic emissions is also unlikely, as phase inversion of the stimulus causes phase inversion of the response (Kemp 1978, Rutten 1980).

More general indications of a cochlear origin are the high physiological vulnerability of otoacoustic emissions (Rutten 1980) and the fact that an electrical correlate to this acoustic effect has been demonstrated in animals (Wit et al 1989). In conclusion: there is enough evidence to consider otoacoustic emissions as a proven epiphenomenon of the normal function of the cochlea.

1.4 Classification of otoacoustic emissions

By definition, any sound that is produced in the cochlea and that can be measured in the external ear canal is an otoacoustic emission (Probst 1990). There are several ways to elicit otoacoustic emissions by acoustic stimuli. The classification most often encountered in the literature (e.g. Kemp et al 1986,

Probst 1990, Probst et al 1991) is based upon these eliciting stimuli. Nonetheless, the different types of otoacoustic emissions are interrelated in many ways (Kemp 1986). Their practical applicability differs considerably, however, which is the reason for the elaboration which follows.

The first type of otoacoustic emissions consists of those which can be recorded without applying any external stimulus. The sounds which are then measurable in the external ear canal are called spontaneous otoacoustic emissions (SOAEs). These consist of (one or more) pure tones which may be considered as oscillations generated by some active oscillator (Bialek and Wit 1984). The phenomenon of 'sound coming out of the ear' (irrespective of origin) was recognized before the actual discovery of emissions in certain extreme cases, and sometimes referred to as "objective tonal tinnitus" (e.g. Glanville et al 1971, Huizing and Spoor 1973). One should bear in mind that even without applying external sound, internal sound sources in the head (vascular noise, joint and muscle movements etc) may be important to the subsistence of these sounds. Spontaneous otoacoustic emissions are found in between 35% and 78% of normal hearing ears, both in children and adults, as well as in animals (Zurek 1981, Fritze 1983, Strickland et al 1985, Kemp et al 1986, Burns et al 1992, Kok et al 1993b, Whitehead et al 1993). This limits their value for practical applications (Kemp et al 1990).

The second type of otoacoustic emissions is elicited by transients, which by their flat frequency spectrum stimulate a large range of the cochlea. Usually, the term transients is used to indicate clicks, though short frequency sweeps (chirps) are a different form, covering a limited range of the frequency spectrum (Neumann et al 1994). In contrast to spontaneous otoacoustic emissions, click evoked otoacoustic emissions are measurable in virtually all normal human ears (Kemp 1978, Rutten 1980, Johnsen and Elberling 1982, Probst et al 1986, Bray and Kemp 1987, Bonfils et al 1988, Kok et al 1993a). They were originally termed "stimulated acoustic emissions" by their discoverer Kemp, though now generally referred to as transient evoked otoacoustic emissions (TEOAEs). Transient evoked otoacoustic emissions enjoy an increasing popularity in clinical practice, e.g. for screening purposes in children (Stevens et al 1990, Kemp and Ryan 1991, Kok et al 1993, White and Behrens 1993). We will discuss their applicability in more detail below (Chapter 3 - 8).

The third type of otoacoustic emissions is elicited by continuous tonal

stimulation, which creates stimulus-frequency otoacoustic emissions (SFOAEs, e.g. Kemp and Chum 1980), also called synchronously evoked otoacoustic emissions (Zwicker and Schloth 1984). The eliciting stimulus is a pure tone that is swept over a limited frequency range. The added acoustical energy from the cochlea results in peaks and valleys in the sound-pressure level of adjacent frequencies. The practical value of SFOAEs is limited (Probst 1990).

The last type of otoacoustic emissions is generated by simultaneously presenting two tones of different frequencies f1 and f2 to the cochlea: this creates distortion products (combination tones) such as f2-f1, 2f1-f2 etc. The latter is called the cubic difference tone, which can be used to obtain information on specific locations of the cochlea (Lonsbury-Martin et al 1990, Probst and Hauser 1990). Distortion product emissions are also called acoustic distortion products (Norton 1992) or intermodulation products (Probst 1990).

A different classification was proposed by Probst et al (1986). They distinguished two types of emissions (short and long), based on the duration of the response and the presence or absence of spontaneous emissions. However, this classification is not widely accepted because of its restricted clinical value.

Another possible method is to classify otoacoustic emissions by the moment of stimulation, i.e. before or during response measurement. Thus, click and transient evoked OAEs belong to the first, stimulus frequency and distortion product emissions to the second category. The technical problems in accurately discriminating responses are accordingly greater in the latter, as the stimulus intensity is much greater than that of the response. Although theoretically sound, the usefulness of this classification is limited. Nonetheless, it shows that in spite of its necessity, any attempt at classification meets practical limitations.

1.5 Equipment for otoacoustic emission measurements

In the early days of otoacoustic emissions measurement, most systems were custom-made and only appropriate for laboratory use (e.g. Kemp 1978, Wilson 1979, Wit and Ritsma 1980). Other systems, such as POEMS (Cope and Lutman 1988), were used at several locations but could not be made commercially available due to patent restrictions. The time required for adequate measurement (1 - 5 minutes, depending on the amplitude of the response) could be further reduced by increasing stimulus rates using maximum length sequences (Lutman 1993, Thornton 1993). These are currently being

implemented into this system (Lutman 1995), which may be marketed in the future. The development of commercially available and reliable systems is still evolving. When comparing these systems, consideration of both hardware and software is important: stimulus possibilities and calibration, averaging and other artifact or noise suppression techniques, probe quality and dimensions, analysis programs, time required for measurements, portability and sturdiness of the system. Apart from these, such factors as price, after sales service, computer and printer requirements may play a role in deciding which system is most suitable. The most vulnerable part of all systems from a practical point of view remains the measuring probe (Kemp et al 1986), which can easily be obstructed by ear wax or dislocated by head movements if not well fitted.

Below is a description of the currently (1995) available systems with reference to the issues mentioned above. These include: 1. ILO88, 2. ILO288 Echoport, 3. ILO92 and 4. Echosensor by Otodynamics Ltd (England), 5. CUBeDIS by Etymotic Research (U.S.A.; distributed by Mimosa Acoustics), 6. Celesta 503 by Madsen Electronics (Norway) and 7. GSI-60 DPOAE by Grason-Stadler (U.S.A.).

1. The ILO88 was the first apparatus that found a widespread use. It was designed by Kemp and his coworker Bray at the Institute of Laryngology and Otology in London (Bray 1989). It offers possibilities for stimulus variation (nonlinear and linear clicks, spontaneous and toneburst evoked otoacoustic emissions). Calibration is easily performed by means of a 2 ml coupler and a given initial response curve for every probe. The nonlinear technique implemented is known as scaled subtraction (Bray 1989): stimuli are delivered in trains of four, with the first three pulses of opposite polarity to the fourth, which is 9.5 dB stronger. This summation of four clicks results in elimination of the linear components of the response, yielding only nonlinear components as OAEs. In default mode, 260 sweeps (of four stimuli) are averaged, but this number may be varied according to circumstances. This averaging procedure enables adequate noise suppression. Artifact rejection is mainly due to windowing the response from 2.5 to 20.5 ms after stimulus start. In the first few milliseconds the otoacoustic emission response is completely obscured by ringing of the middle ear. Besides, a continuous monitoring of the stimulus level is available during testing procedures. The probes are relatively

vulnerable, being manipulated into patients ears and exposed to ear wax and other debris. Fortunately, disposable tips have been introduced which eliminate the need of time-consuming cleansing procedures under the microscope, a necessity in earlier days. There are two sizes: adult and infant probes. Analysis possibilities include frequency band analysis, comparison with other responses etc. Time required for measurement averages about 2 minutes per ear. The system is meant for fixed base working, linked to a personal computer.

2. The ILO288 Echoport is derived from the ILO88, as its name implies. Stimulus and averaging features are the same. Its main advantages are the so-called Super-QuickScreen mode for fast screening procedures (up to 4x faster than ILO88), and its portability, which in a neonatal clinical setting is vital for efficient use. Furthermore, a better devised neonatal probe has been added.

3. The ILO1088 Echosensor is an even more compact device which needs no (separate) computer. It has simple but well documented interpretation criteria to determine whether or not otoacoustic emissions are present, exploring the 1.5- 3.5 kHz frequencies. Obviously, its possibilities of analysing responses or modifying stimuli are very limited. This system is meant for off-site newborn screening, but may be fitted with an adult probe (with disposable tip) as well.

4. The ILO92 may be regarded as an extended version of the ILO88: not only spontaneous and click evoked otoacoustic emissions can be assessed, but distortion product emissions as well. Moreover, various sophisticated analytic procedures are possible with this system. The software is regularly being upgraded.

5. The CUBeDIS distortion product measurement system has been on the market for several years now and is, as its name implies, designed for DP measurements (see Chapter1.4). However, with adapted software, TEOAEs can also be assessed. The main stimulus parameters that can be varied are the minimum and maximum of the f2 frequency range, the sound pressure levels of f1 and f2, and the f2/f1 ratio. Continuous measurements with fixed conditions are possible for monitoring purposes. A DB-100 artificial ear (Zwislocki coupler) can be used for calibration. Averaging time can be varied,

but no specification is given of artifact rejection techniques implemented. The probe of this device contains two sound tubes and a microphone, and is available in different sizes (adult and newborn) with disposable foam ear tips. Analysis options are multiple, and data can be easily converted to a simple format for import into a spreadsheet. The system is not designed to be portable.

6. The Celesta 503 is one of the most recently marketed systems, suitable for measurement of spontaneous, transient evoked and DP otoacoustic emissions. Its possibilities for stimulus variation are comparable to the ILO92, and it uses the same scaled subtraction technique for noise suppression. The probe's design is derived from a behind the ear hearing aid; it can be completely disassembled for easy cleaning. Besides, it can be mounted on a shoulder harness or headband for better stability. Analysis options are not well documented, although the software can be updated with newly developed test features. The system can be connected to a portable IBM or compatible personal computer.

7. The GSI 60 DPOAE system is similar in design to the Celesta but, as its name implies is only suitable for distortion product measurements. Apart from being new, it offers no advantages over the other systems described.

As already mentioned, the 'very best' otoacoustic emissions measurement system depends on many parameters. On the whole however, the ILO88 and ILO92 systems in our opinion have definite advantages because of their well devised probe, extensive analysis possibilities, and their excellent after sales service.

1.6 Clinical applications of otoacoustic emissions

The possibilities of using otoacoustic emissions in audiological practice depend on a number of variables: 1. the population under study (infants, adults), 2. the available equipment, 3. the type of emissions measured, 4. the purpose of the measurement (screening, threshold assessment, differential diagnosis), and of course, 5. the availability of other audiometric tests.

1. The population under study is an important factor which influences the clinical applicability of otoacoustic emissions. In infants and children,

cooperation is often limited, which reduces the available time for measurement unless sedatives or anaesthetics are used. Here otoacoustic emissions show definite advantages as compared to behavioral methods, although the latter are more suitable for accurate threshold measurements. In the NIH consensus on infant hearing screening (Anon 1993), confirmation of a suspected hearing loss by brain stem audiometry is therefore advised, thereby following the conclusion of Stevens et al (1989, 1990). The a priori chance of hearing impairment in the screening population determines the degree of specificity and sensitivity needed for optimal benefit from the screening. These expected values are more varied in an adult population where there is one challenging possibility the children setting usually lacks: comparison with pure tone audiometry.

2. As to the equipment available, we refer to the preceding paragraph.

3. The type of otoacoustic emissions assessed is important, as there are large differences in prevalence in both normal and hearing impaired ears (see Chapter1.4). Being the 'most original' kind of otoacoustic emissions, click evoked OAEs are still most popular for infant screening purposes. For example, as a result of the large scale testing of infants for hearing impairment in Rhode Island (RIHAP, see White and Behrens 1993), the National Institutes of Health (NIH) agreed that all infants in the USA should be screened by (click evoked) otoacoustic emissions (Anon 1993). In other countries such a conclusion has not yet reached scientific and governmental support. Another unsolved issue concerns the so-called 'DP-gram' or 'distortion product audiogram': a supposedly frequency specific mapping of cochlear status by means of distortion product otoacoustic emissions (Lonsbury-Martin et al 1990). This frequency specificity is in question (e.g. Probst et al 1993), as is the underlying mechanism of DPOAEs, which may be very different from that of other emissions. The practical usefulness of spontaneous and stimulus frequency otoacoustic emissions is limited (Kemp et al 1990). Their main purpose is for research.

4. The purpose of the measurement can be either exclusion of socially significant hearing impairment (yes/no) or assessment of hearing threshold (how much?) in a range of frequencies or differential diagnosis (what or how?). If we

are interested in detecting hearing loss or no hearing loss, otoacoustic emissions are generally acknowledged as being useful. As Kemp et al (1986) put it: "Acoustic cochleography does not quantify hearing loss, it detects its presence". The determination of the exact hearing thresholds (quantification) can be very difficult in case of psychogenic hearing loss or malingering, if tests are used which require cooperation from the subject (like the pure tone audiogram). Even in 'normal' testing situations we should be aware that the outcome of a measurement is a number that has a certain probability of indicating the real value (of the threshold). Of course, the more accurate our measurement, the higher this probability. Nonetheless, two subjective sources of inaccuracy are involved (subject and interpreter).

In differential diagnosis the main question is whether the hearing loss is localized in the external or middle ear, the inner ear (cochlea), the neural part of the auditory system (cochlear nerve or nuclei) or 'between the ears' (psychogenic). Not only the localization, but also the cause of the hearing loss may be of interest (Menière's disease or noise-induced, otitis media with effusion or otosclerosis, etc). An issue that links both aspects of quantification and of qualification (diagnosis) is the degree of frequency specificity of any given hearing test. The importance of this phenomenon is derived directly from the already mentioned frequency specificity of the cochlea. As stated above, some authors believe that the frequency specificity of DPOAEs is similar to that of the audiogram (Martin et al 1990), although this is doubted by others (e.g. Norton 1992). The same frequency specificity was found by some authors for TEOAEs (e.g. Prieve et al 1993), though not by others (e.g. Probst et al 1987).

5. The audiometric tests generally in use comprise the pure tone audiogram as a 'golden standard', speech audiometry, Békésy audiometry, tympanometry (middle ear impedance assessment), auditory brain stem response, stapedius reflex measurements, electrocochleography, and a number of other tests (alternate binaural loudness balance, tests of 'central' auditory function). Each of these tests has specific advantages and shortcomings in assessing the amount and kind of hearing loss (e.g. Rodenburg 1989). A special kind of assessment concerns the measurement of tinnitus. The ususal way of measuring tinnitus levels and frequencies is by contralateral matching. However, in quantitative aspects, the pure tone audiogram remains the most important for daily practice.

1.7 Objectives of this study

We intended to define the value of click evoked otoacoustic emission (OAE) measurement in general audiological practice, as compared to pure tone audiometry. The issues studied are described in the following chapters, each covering one of these questions:

1. What practical aspects are important when measuring click evoked OAEs?
2. What level of OAEs is found in normal ears?
3. What is the influence of middle ear function on OAEs?
4. Is there an effect of age on OAEs?
5. Are OAEs useful in differential diagnosis?
6. What happens to OAEs when hearing varies with frequency or with time?
7. Is there a correlation between subjective tinnitus level and OAEs?

References

Anon (1993): Early identification of hearing impairment in infants and young children. NIH Consensus Statement 11(1):1-24

Békésy G von (1939): Über die mechanisch-akustischen Vorgänge beim Hören. Acta Otolaryng 27:281-297 and 388-396

Bialek WS, Wit HP (1984): Quantum limits to oscillator stability: theory and experiments on acoustic emissions from the human ear. Phys Lett 104A:173-178

Bonfils P, Piron JP, Uziel A, Pujol R (1988): A correlative study of evoked otoacoustic emission properties and audiometric thresholds. Arch Otorhinolaryngol 245:53-56

Bray PJ (1989): Click evoked otoacoustic emissions and the development of a clinical otoacoustic hearing test instrument:1-201. Thesis, Univ. London

Bray PJ and Kemp DT (1987): An advanced cochlear echo technique suitable for infant screening. Br J Audiol 21:191-204

Brownell WE (1983): Observations of a motile response in isolated outer hair cells. In Webster WR and Atkin LM (eds): Mechanisms of hearing:5-10. Monash Univ Press, Clayton, Australia

Brownell WE, Bader CR, Bertrand D, de Ribaudpierre Y (1985): Evoked mechanical responses of isolated cochlear outer hair cells. Science 227:194-196

Burns EM, Arehart KH, Campbell SL (1992): Prevalence of spontaneous otoacoustic emissions in neonates. J Acoust Soc Am 91:1571-5

Cope Y, Lutman ME (1988): Oto-acoustic emissions. In McCormick B (ed) Paediatric audiology 0-5 years:221-246. Tailor and Francis, London

Dallos P (1992): The active cochlea. J Neurosc 12(2):4575-85

Elliott E (1958): A ripple effect in the audiogram. Nature 181:1076

Flock Å, Cheung H (1977): Actin filaments in sensory hair cells of inner ear receptor cells. J Cell Biol 75:339-343

Flottorp G (1953): Pure-tone tinnitus evoked by acoustic stimulation: the idiophonic effect. Acta Otolaryngol 43 :396-415

Fowler EP (1949): Standard audiogram recording. Acta Otolaryngol Suppl 78:173-182

Fritze W (1983): Registration of spontaneous cochlear emissions by means of Fourier transformation. Arch Otorhinolaryngol 238:189-196

Glanville JD, Coles RRA, Sullivan BM (1971): A family with objective high-tonal tinnitus. J Laryngol Otol 85:1-10.

Gold T (1948): Hearing II. The physical basis of the action of the cochlea. Proc Roy Soc (Biol) 135:492-498

Hemholtz H (1863): Ueber die Wahrnehmung der Klangfarben. In: Die Lehre von den Tonempfindungen als physiologische Grundlage für die Theorie der Musik:182-223. Braunschweig.

Huizing EH, Spoor A (1973): An unusual type of tinnitus. Arch Otolaryngol 98:134-136

Hudspeth AJ (1989): How the ear's works work. Nature 341:397-404.

Johnsen NJ, Elberling C (1982): Evoked acoustic emissions from the human ear II: normative data in young adults and influence of posture. Scand Audiol 11:69-77

Kemp DT (1978): Stimulated emissions from within the human auditory system. J Acoust Soc Am 64(5):1386-1391

Kemp DT (1979a): Evidence of mechanical nonlinearity and frequency selective wave amplification in the cochlea. Arch Otorhinolaryngol 224:37-45

Kemp DT (1979b): The evoked cochlear mechanical response and the auditory microstructure: evidence for a new element in cochlear mechanics. Scand Audiol Suppl 9:35-47

Kemp DT (1981): Physiologically active cochlear micromechanics - one source of tinnitus. In: Evered D, Lawrenson G (eds) Tinnitus: Ciba Foundation Symposium 85:54-81. London, Pitman

Kemp DT (1986): Otoacoustic emissions, travelling waves and cochlear mechanisms. Hear Res 22:95-104

Kemp DT, Bray P, Alexander L, Brown AM (1986): Acoustic emission cochleography - practical aspects. Scand Audiol Suppl 25:71-95

Kemp DT, Chum R (1980): Properties of the generator of stimulated otoacoustic emissions. Hear Res 2:213-232

Kemp DT, Martin JA (1976): Active resonant systems in audition. In: 13th International Congress of Audiology (Florence) Abstracts:64-65. Geneva, International Society of Audiology.

Kemp DT, Ryan S (1991): Otoacoustic emission tests in neonatal screening programmes. Acta Otolaryngol Suppl 482:73-84

Kemp DT, Ryan S, Bray P (1990): A guide to the effective use of otoacoustic emissions. Ear Hear 11:93-105

Kok MR, van Zanten GA, Brocaar MP, Wallenburg HCS (1993a): Click-evoked otoacoustic emissions in 1036 ears of healthy newborns. Audiol 32:213-224

Kok MR, van Zanten GA, Brocaar MP (1993b): Aspects of spontaneous otoacoustic emissions in healthy newborns. Hear Res 69:115-123

Lim DJ (1986): Cochlear micromechanics in understanding otoacoustic emission. Scand Audiol Suppl 25:17-25

Lonsbury-Martin BL, Harris FP, Stagner BB, Hawkins MD, Martin GK (1990): Distortion product emissions in humans. I. Basic properties in normally hearing subjects. Ann Otol Rhinol Laryngol Suppl 147:3-14

Lutman ME (1993): Recording click-evoked otoacoustic emissions at very high stimulus rates. Abstr Int Congr OAE Lyon

Lutman ME (1995): personal communication.

Martin GK, Ohlms LA, Franklin DJ, Harris FP, Lonsbury-Martin BL (1990): Distortion product emissions in humans. III. Influence of sensorineural hearing loss. Ann Otol Rhinol Laryngol Suppl 147:30-42

Neumann J, Uppenkamp S, Kollmeier B (1994): Chirp evoked otoacoustic emissions. Hear Res 79(1-2):17-25

Norton SJ (1992): Cochlear function and otoacoustic emissions. Semin Hear 13:1-14

Prieve BA, Gorga MP, Schmidt A, Neely S, Peters J, Schultes L, Jestaedt W (1993): Analysis of transient-evoked otoacoustic emissions in normal-hearing and hearing-impaired ears. J Acoust Soc Am 93(6):3308-3319

Probst R (1990): Otoacoustic emissions: an overview. Adv Otorhinolaryngol 44:1-91

Probst R, Coats AC, Martin GK, Lonsbury-Martin BL (1986): Spontaneous, click-, and toneburst-evoked otoacoustic emissions from normal ears. Hear Res 21:261-275

Probst R, Lonsbury-Martin BL, Martin GK, Coats AC (1987): Otoacoustic emissions in ears with hearing loss. Am J Otolaryngol 8:73-81

Probst R, Hauser R (1990): Distortion product otoacoustic emissions in normal and hearing-impaired ears. Am J Otolaryngol 11:236-243

Probst R, Lonsbury-Martin BL, Martin GK (1991): A review of otoacoustic emissions. J Acoust Soc Am 89:2027-2067

Probst R, Harris FP, Hauser R (1993): Distortion product otoacoustic emissions- an overview of their clinical applications. Abstr Int Congr OAE Lyon

Rodenburg M (1989): Audiometrie: methoden en klinische toepassingen. Coutinho, Muiderberg

Rutten WLC (1980): Evoked acoustic emissions from within normal and abnormal human ears: comparison with audiometric and electrocochleographic findings. Hear Res 2:263-271

Sellick PM, Patuzzi R, Johnstone BM (1982): Measurement of basilar membrane motion in the guinea pig using the Mössbauer technique. J Acoust Soc Am 72:131-141

Siegel JH, Kim DO (1982): Efferent neural control of cochlear mechanics? Olivocochlear bundle stimulation affects cochlear biomechanical nonlinearity. Hear Res 6:171-182

Spoendlin H (1986): Receptoneural and innervation aspects of the inner ear anatomy with respect to cochlear mechanics. Scand Audiol Suppl 25:27-34

Stevens JC, Webb HD, Hutchinson J, Connell J, Smith MF, Buffin J (1989): Click evoked otoacoustic emissions compared with brain stem electric response. Arch Dis Child 64:1105-1111

Stevens JC, Webb HD, Hutchinson J, Connell J, Smith MF, Buffin J (1990): Click evoked otoacoustic emissions in neonatal screening. Ear Hear 11:128-133

Strickland EA, Burns EM, Tubis A (1985): Incidence of spontaneous otoacoustic emissions in children and infants. J Acoust Soc Am 78:931-935

Thornton ARD (1993): New techniques in recording click-evoked emissions. Abstr Int Congr OAE Lyon

Ward WD (1955): Tonal monaural diplacusis. J Acoust Soc Am 27(2):365-372

Wegel RL (1931): A study of tinnitus. Arch Otolaryngol 14:158-165

White KR, Behrens TR (eds) (1993): The Rhode Island hearing assessment project: implications for universal newborn hearing screening. Seminars in Hearing 14(1):1-122

Whitehead ML, Kamal N, Lonsbury-Martin BL, Martin GK (1993): Spontaneous otoacoustic emissions in different racial groups. Scand Audiol 22:3-10

Wilson JP (1979): Recording of the Kemp echo and tinnitus from the ear canal without averaging. Proc Physiol Soc 19(2):8-9

Wilson JP (1980): Evidence for a cochlear origin for acoustic re-emissions, threshold fine-structure and tonal tinnitus. Hear Res 2:233-252

Wit HP, Langevoort JC, Ritsma RJ (1981): Frequency spectra of cochlear acoustic emissions ("Kemp-echoes"). J Acoust Soc Am 70(2):437-445

Wit HP, Ritsma RJ (1979): Stimulated acoustic emissions from the human ear. J Acoust Soc Am 66(3):911-913

Wit HP, Van Dijk P, Segenhout JM (1989): An electrical correlate of spontaneous otoacoustic emissions in a frog, a preliminary report. In: Wilson JP et al (eds) Cochlear mechanisms; structure, function and models. New York, Plenum

Zenner HP, Zimmermann U, Schmitt U (1985): Reversible contraction of isolated mammalian cochlear hair cells. Hear Res 18:127-133

Zurek PM (1981): Spontaneous narrow-band acoustic signals emitted by human ears. J Acoust Soc Am 69:514-523

Zwicker E (1983): Delayed evoked oto-acoustic emissions and their suppression by Gaussian-shaped pressure impulses. Hear Res 11:359-371

Zwicker E, Schloth E (1984): Interrelation of different oto-acoustic emissions. J Acoust Soc Am 75:1148-1154

▸ 2 SUBJECTS AND METHODS

2.1 Introduction

In this chapter a general description is given of three aspects of this study: who, what and how we measured. In the following chapters, additional details on these issues will be given when appropriate. In this way, we strived to minimize redundancy without compromising legibility. The underlying question in this chapter is the first issue mentioned in the introduction (Chapter 1.7): what practical aspects are important when measuring click evoked otoacoustic emissions?

2.2 Subjects

The setting of the present study was the Department of Otorhinolaryngology (section Audiology) of the University Hospital Utrecht. Between November 1989 and March 1992 a total of 500 subjects (1000 ears) were studied. First, as a control group, fifty adult volunteers under 25 years of age, with normal hearing and a negative otological history, were asked to have their ears measured. They were mainly medical students and members of the staff of the Department. Secondly, a large group of patients presenting with complaints related to hearing loss were examined. Although we did not exclude children, we concentrated on adults in this study: thus they formed the major part of our study population. Some patients were referred to the Department by the Central Military Hospital situated nearby.

There was a random selection of patients (apart from their complaints of hearing loss), in order to get an adequate impression of otoacoustic emission measurement in general audiological practice. In a small percentage of the patients, pure tone audiometry was impossible due to several factors (young age, lack of cooperation, mental retardation). In one case only, otoacoustic emissions could not be measured in a subject, due to probe fitting difficulties.

The age distribution of the subjects (patients and normal hearing controls) is visualized in Figure 2.1. Ages ranged from 0 to 85 years with an approximately normal distribution in the patient group. The control group was comprised of a limited age range. The gender distribution of the patients was fifty-fifty; in the control group there was a slight female predominance (see also Chapter 3).

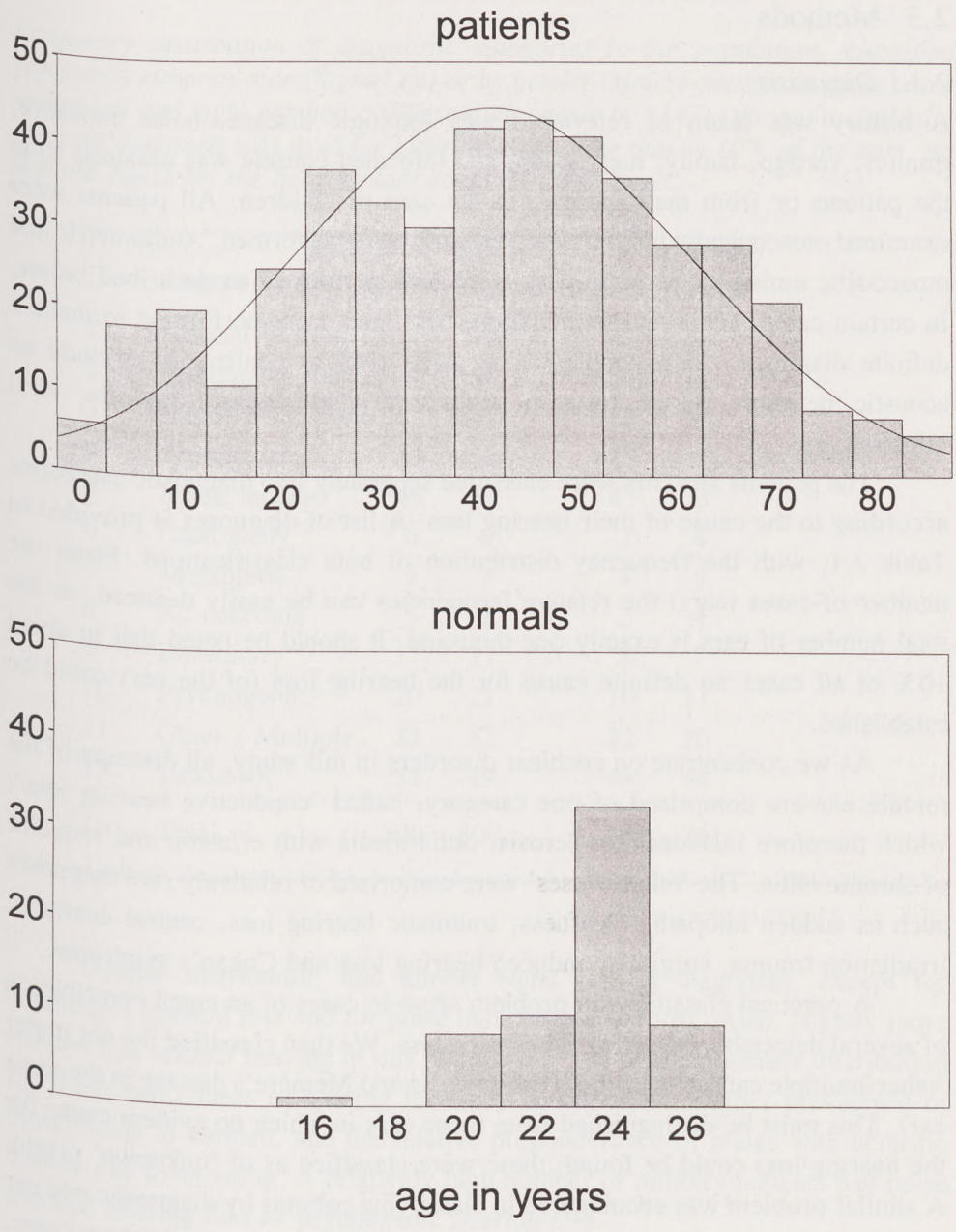


Figure 2.1

Frequency distribution by age of the studied populations of 439 patients and 61 normal hearing controls. Note the approximately normal distribution of ages in the patient group.

2.3 Methods

2.3.1 Diagnosis

A history was taken of relevant issues (otologic disease, noise exposure, tinnitus, vertigo, family, medication) and informed consent was obtained from the patients or from their parents, in the case of children. All patients were examined otoscopically before measurements were performed. Audiometric and otoacoustic emission measurements were then performed as described below. In certain cases, additional (non-audiometric) tests were performed to make a definite diagnosis; for example CT or MRI scan to confirm or exclude an acoustic neuroma, blood tests to exclude thyroid disease, syphilis, viral infection, etc.

The patients and ears were classified separately into diagnostic categories according to the cause of their hearing loss. A list of diagnoses is provided in Table 2.1, with the frequency distribution of both classifications. From the number of cases (ears) the relative frequencies can be easily deduced, as the total number of ears is exactly one thousand. It should be noted that in about 10% of all cases no definite cause for the hearing loss (of the ear) could be established.

As we concentrate on cochlear disorders in this study, all diseases of the middle ear are comprised of one category, called 'conductive hearing loss', which therefore includes otosclerosis, otitis media with effusion and sequelae of chronic otitis. The 'other causes' were comprised of relatively rare diagnoses such as sudden idiopathic deafness, traumatic hearing loss, central deafness, irradiation trauma, surgically induced hearing loss and Cogan's syndrome.

A practical classification problem arose in cases of an equal contribution of several detectable causes to the hearing loss. We then classified the ear under 'other/multiple causes' (e.g. both presbycusis and Menière's disease in the same ear). This must be distinguished from those ears in which no evident cause for the hearing loss could be found: these were classified as of 'unknown' origin. A similar problem was encountered in classifying patients by diagnosis: one ear may be normal, but the other may show an acoustic trauma, etc. In these cases, the main clinically relevant diagnosis was chosen for the patient.

Age distribution varied considerably according to diagnosis, which reminds us of the interrelatedness of these two parameters (see Figure 2.2).

Table 2.1 DIAGNOSIS IN 1000 EARS AND 500 PATIENTS

Frequency distribution of diagnostic categories in the population, classified separately either by side (Right/Left) or by gender (Male/Female). In those cases where left and right ear had a different diagnosis (n=147), the main clinically relevant diagnosis was used for classification. Note that in 10% of the ears, no definite cause for the hearing loss could be determined.

	diagnosis	R	L	M	F
1	Normal hearing	145	134	42	60
2	Conductive loss	71	80	26	48
3	Menière's disease	57	47	32	32
4	Presbycusis	43	53	15	16
5	Noise induced	46	52	41	0
6	Ototoxicity	6	6	2	4
7	Meningitis	6	7	4	5
8	Ac neuroma	5	2	2	4
9	Hereditary	17	17	5	7
10	Psychogenic	20	21	10	11
11	Other / Multiple	32	32	22	20
12	Unknown	52	49	48	44
	Total	500	500	249	251

Gender distribution was almost equal for all diagnoses, except for conductive hearing loss and for noise induced hearing loss. Also, slightly more women had normal hearing in this population. The unequal gender distribution for these two causes of hearing loss may be due to the higher prevalence of otosclerosis in women, and the relative preponderance of males with acoustic trauma due to shooting. A relatively high number of military patients had noise induced hearing loss or psychogenic hearing loss.

In 71% of the cases (353/500) both ears had the same diagnosis. In the 29% where there was a difference between right and left ear diagnosis, the most common diagnoses were (R/L): normal hearing (29/22%), Menière's disease (16/9%) or unknown origin (15/13%), respectively.

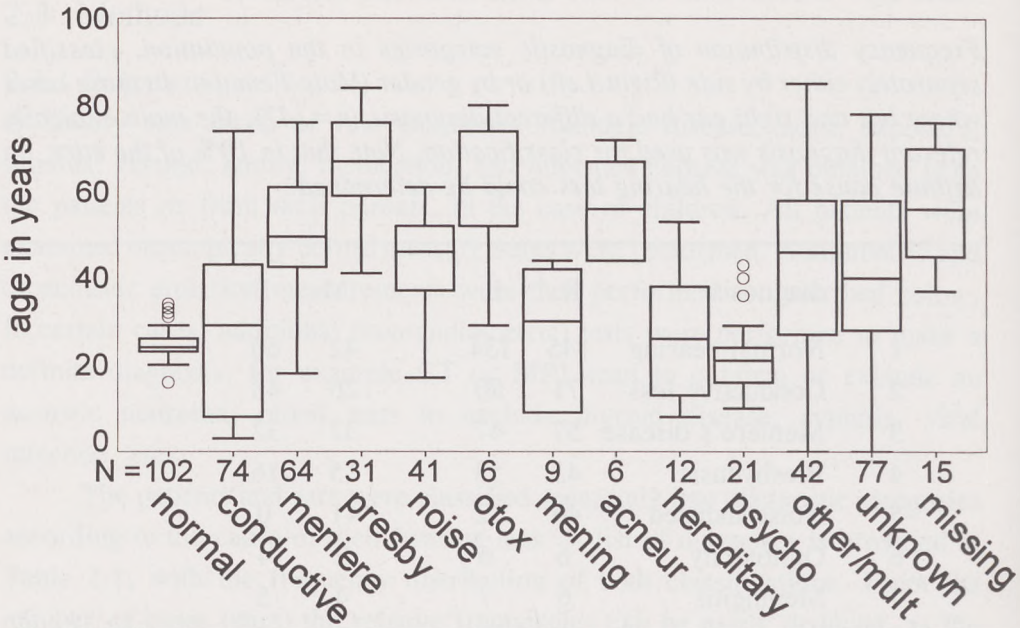


Figure 2.2

Age distribution of patients and normals by diagnostic group, showing large differences in pattern. This indicates the interrelatedness of these parameters. The bars indicate median values; 50% of cases have values within the box. The number of subjects (N) is noted below each box. The diagnostic groups are: normal hearing, conductive hearing loss, Menière's disease, presbycusis, noise induced hearing loss, ototoxicity, meningitis, acoustic neuroma, hereditary loss, psychogenic loss, other/multiple causes, unknown etiology. The last group comprises missing values.

2.3.2 Hearing assessment

Measurements were carried out in a double walled, sound attenuating chamber, with the equipment for the otoacoustic emissions installed outside, and with the researcher in visual contact with the subject. This setting was chosen to eliminate the noise source from the personal computer. In a few cases, if patients were unable to be moved into the audiometry cabin, bedside measurements were taken, resulting in higher background noise levels with equivalently less reliable responses. However, we found that good probe fitting could overcome part of this impediment for the otoacoustic emission assessment. All measurements were performed by adequately trained personnel.

Pure tone audiometry (PTA) data was collected using headsets with Madsen OB 822 audiometers which were regularly checked for appropriate calibration (ISO 1964). Pure tone thresholds for standard octave frequencies

(0.125 to 8 kHz) were assessed, as described in detail in the introduction (Chapter 1.1). In cases of large interoctave differences in threshold, additional thresholds were measured at 1.5, 3 and 6 kHz. If there was a suspicion of middle ear pathology, tympanometry was performed using a standard tympanometer (American Electromedics Corporation model 85 AR). In deaf ears, for statistical purposes, a value of 130 dB HL was imputed for hearing thresholds. Usually, in ears with apparently normal hearing (air conduction thresholds of 10 dB HL or less), no bone conduction thresholds were measured.

2.3.3 Otoacoustic emission measurement

As mentioned in the introduction (Chapter 1.5) there are different ways of eliciting OAEs, and different systems have been developed for these purposes. Some of these are only for laboratory use, others are commercially available. The otoacoustic emission data in this study were obtained by means of the commercially available ILO88 Otodynamic Analyzer system as designed by Kemp and coworkers (Kemp et al 1990), linked to a Laser 286/3 personal computer. The choice for this device was based on its practical design, its extensive possibilities for analysis, and its proven applicability in non-laboratory settings. A schematic representation of the setup is given in Figure 2.3.

The ILO88 system consists of a pulse generator and attenuator, linked to a miniature sound source. Together with a miniature microphone this forms a probe, fitting into the external ear canal (like the probe of a tympanometer). Acoustic stimuli are delivered to the ear and the responses are led to an amplifier and a processing board, which averages the responses. After completion of the procedure, they are visualized on the screen of the personal computer.

The stimuli used to elicit otoacoustic emissions were 80 micro second rectangular pulses presented at a rate of 20 per second at 80 dB SPL (default nonlinear mode). This resulted in an approximately flat stimulus spectrum from 0.5 to 5 kHz. Due to variations in meatal volume, probe positioning, etc. some variation in both spectrum and amplitude of the stimuli occurred. As OAEs are a nonlinear phenomenon, these variations will not significantly influence the responses obtained (regression statistics revealed that only 9% of response variability was caused by stimulus factors). Stimuli were delivered in groups of

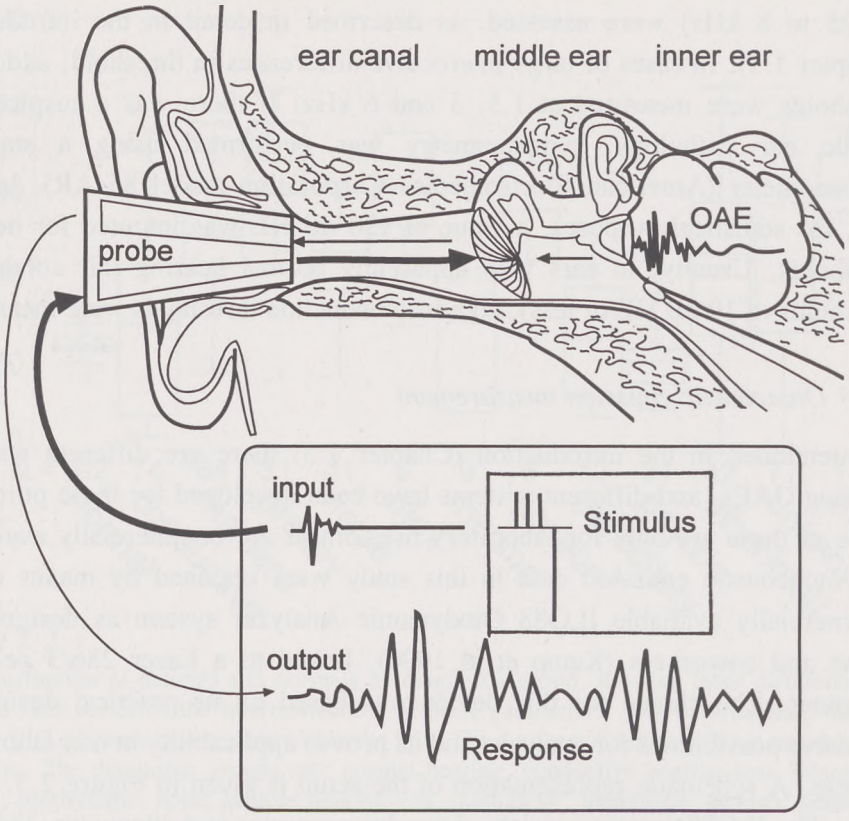


Figure 2.3

Schematic representation of the OAE measurement setup (modified after Kemp 1979). The stimuli are sequences of four electrical pulses yielding clicks with a broadband frequency spectrum. This sound reaches the cochlea through a well-fitted probe, the ear canal and the middle ear. The normally functioning inner ear (cochlea) responds with a very soft 'echo' (otoacoustic emission or OAE) which travels back into the ear canal. There it is picked up by a sensitive microphone (also in the probe). The signal is processed (amplified and averaged) and made visible on the screen of the personal computer.

four, with the first three pulses of opposite polarity to the fourth, which was 9.5 dB greater in amplitude than the previous three periods. This method, the scaled subtraction technique (Bray 1989), results in elimination of linear components of the response. During each measurement, the stimulus level and probe position were constantly checked by visual control on the screen and on the patient. In cases of a stimulus stability of less than 80%, the measurement was repeated. The system was regularly calibrated with a 2 ml coupler.

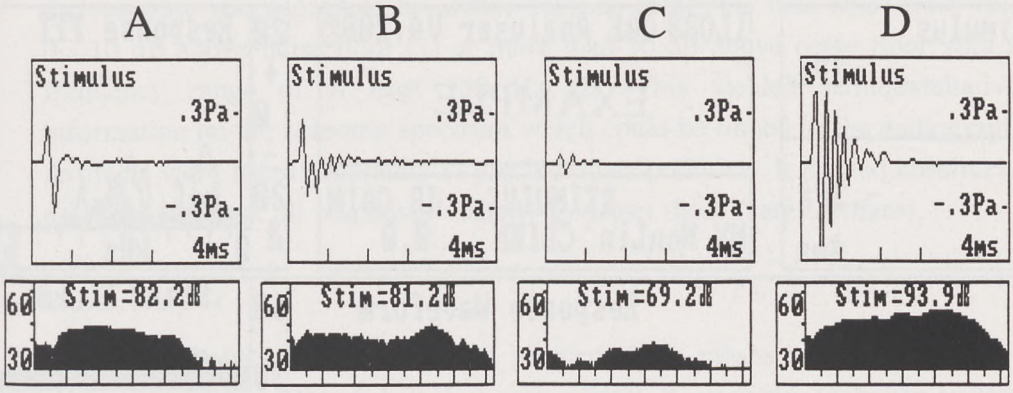


Figure 2.4

Different forms of acoustic stimuli in the ear canal, elicited by electrical rectangular pulses via the probe. An adequate stimulus has 1-2 deflections with an approximately flat spectrum, and an amplitude of more than 0.15 Pa (A). If the external ear canal is not well sealed, the stimulus will be less adequate and show resonance peaks (B). If the probe is placed against the ear canal wall, an inadequate stimulus will result with an amplitude less than 0.1 Pa (C). A similarly inadequate fit with air leakage may result in ringing and an amplitude exceeding 0.3 Pa, as displayed in the last figure (D). A is considered a 'good' stimulus, B 'dubious' and C and D are scored 'insufficient'. The exact classification criteria are mentioned below.

To classify the 'input' into the ear, the stimulus form was scored as good, dubious or insufficient (see Figure 2.4 for examples). The criteria for a 'good' stimulus were: 1-2 deflections, amplitude more than 0.15 Pa. A 'dubious' stimulus had 3 or more deflections but an amplitude not exceeding 0.3 Pa. An 'insufficient' stimulus had either more than 8 deflections with an amplitude of more than 0.3 Pa, or only one hardly visible deflection with an amplitude less than 0.1 Pa. Both these stimulus deformations result in inadequate measurements. In this way, we attempted to semiquantitatively score the effects of probe fitting on stimulus level and spectrum.

The noise level was monitored continuously during each measurement, and generally was less than 40 dB SPL (mean 37 $\pm$ 4 dB). In very noisy measurements, the artifact rejection system would act as a safeguard against incorporating contaminated sweeps. The percentage of correct sweeps ranged from 6 to 100% with a median of 87%. Usually, 260 accepted sweeps were averaged for further analysis, requiring about one to two minutes recording time. In normal ears, less sweeps would suffice to obtain adequate responses.

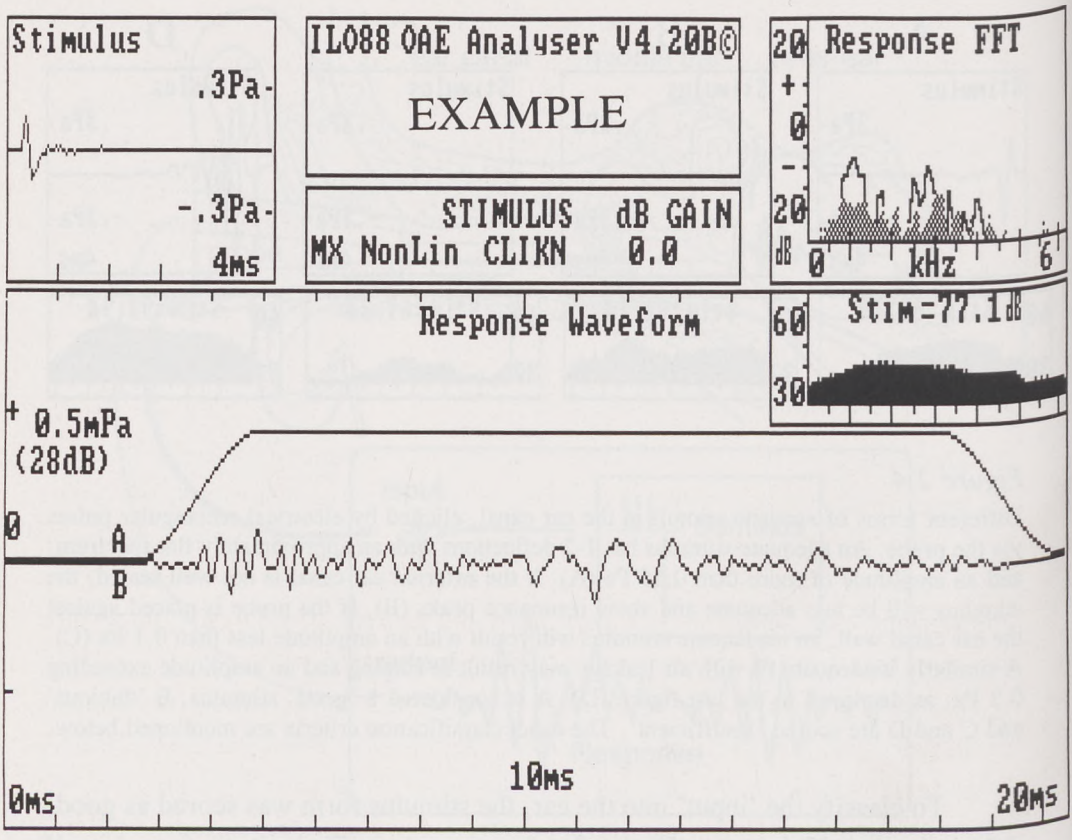


Figure 2.5

Example of an otoacoustic emission response, windowed from 2.5 to 20.5 msec after stimulus start. Note the stimulus form (top left) and response spectrum (top right).The stimulus spectrum is shown below the response, for better comparison. The scales of stimulus and response are quite different.

The response obtained was windowed from 2.5 to 20.5 msec after the start of the stimulus, as illustrated in Figure 2.5. The main parameters analyzed were: the mean sound level of the response (ECHO, in dB SPL) and the reproducibility of the response (REPRO, in percentages). This figure indicates the shape similarity between the responses of two buffers, and is computed as the cross-correlation coefficient between the two waveforms.

For a more frequency-specific analysis of the response spectrum, the following frequency bands were visually analyzed: 0.5 to 1 kHz, 1 to 2 kHz, 2 to 4 kHz and 4 to 6 kHz. In each of these bands, the signal to noise ratio of

the response was scored on an offline basis as being less than noise floor (0), 0 - 10 dB above noise floor (1) or more than 10 dB above noise floor with a frequency range of at least 150 Hz (2). This yielded semiquantitative information on the response spectrum which could be linked to the audiogram. Artifacts were noted separately to preclude data pollution. It proved absolutely essential to check all responses visually to detect these (rare) artifacts.

2.3.4 Analysis

Statistical analysis of the data was performed by means of the SPSS/PC+ package (versions 4.0 to 6.1.2). For each subject, 87 variables including system variables were recorded. A list of these is given in the appendix to this chapter. In a subgroup of the Menière patients, 128 variables were recorded during repeated measurements. Frequency tables, crosstabulation statistics, correlation and regression plots were used, and multivariate analysis was performed when appropriate (see following Chapters). In the course of analysis, it became apparent that a lot of correlations should be interpreted with care.

There are two points to be highlighted in this respect: the processing of missing values, and the cross-correlations between different variables studied. In a large pool of data like the one under study, a certain percentage of the variables contains missing values, for example because a measurement was not performed or not possible (e.g. no bone conduction threshold in a normal ear, no measureable hearing threshold at all in a deaf ear). In these cases, there are several options. First, rather than limiting ourselves to complete-case analysis ('listwise deletion'), available-case analysis was performed ('pairwise deletion'). In this way, all observations of the non-missing variables under study were entered into the analysis.

Secondly, various imputation techniques may be applied (Little and Rubin 1987, Van Buuren et al 1995). For example, in ears with no measurable hearing at a certain frequency, a threshold value of 130 dB HL was imputed. In many cases of tinnitus, a linear interpolation or heuristic extrapolation of hearing thresholds was performed to estimate the threshold at the frequency of the tinnitus, if this did not coincide with a standard audiometric frequency. Whatever method is followed, this creates a bias in the remaining data, which may influence the outcome of any analysis. We found that in most areas of interest, sufficient data were available to ensure a reasonably valid statistical

basis, though it is very hard to estimate the amount of distortion caused by unavailable data.

Another aspect of our material, worthy of consideration, is the relation between different variables. For example, the otoacoustic emission data show a high correlation between different aspects of the responses (overall level, reproducibility). The same holds true for the hearing thresholds across frequencies. The diagnostic categories used are also, in a varying degree, based on the audiometric findings (high- or low frequency loss, etc). Unfortunately, though clinically relevant and clear-cut, they are not mutually exclusive, which sometimes creates classification problems as described above (2.3.1).

A very specific correlation is caused by the fact that one ear is always on the left, the other on the right side of the head. This implies that left and right ears may be compared as groups, or individually (pairwise), with possibly different outcomes (e.g. Van Houwelingen et al 1995). This issue emerges again in Chapter 3. In spite of all these 'logistic distortion products' however, we found that "if you torture the data long enough, it will eventually confess..."

2.4 Conclusion

It proved relatively easy to obtain valid data on click evoked otoacoustic emissions in an adult population. The interpretation of the data, especially the comparison with classical pure tone audiometry, required a solid statistical approach.

References

Bray PJ (1989): Click evoked otoacoustic emissions and the development of a clinical otoacoustic hearing test instrument:1-201. Thesis, Univ. London

Buuren S van, Mulligen E van, Brand J (1995): Omgaan met ontbrekende gegevens in statistische databases: multiple imputatie in HERMES. Kwantitatieve methoden 16(50):5-15

Houwelingen JC van, Stijnen Th, Strik R van (1995): Inleiding tot de medische statistiek. Bunge, Utrecht

Kemp DT (1979): Evidence of mechanical nonlinearity and frequency selective wave amplification in the cochlea. Arch Otorhinolaryngol 224:37-45

Kemp DT, Ryan S, Bray P (1990): A guide to the effective use of otoacoustic emissions. Ear Hear 11:93-105

Little RJA, Rubin DB (1987): Statistical analysis with missing data. Wiley, New York.

Appendix: list of variables used in data analysis

CASENR	case number (1-999)
SEXE	sexe (M/V)
AGE	age in years (0-99)
MEDIC	medication (P=pain A=antibiot O=other G=none)
LAWAAI	noise exposure (Y/N)
DIAG	diagnosis (-1 to 10, 0=unknown)
SUIS_R	tinnitus (Y/N)
NIV_R	level of tinnitus dB (0-99)
FREQ_R	frequency tinnitus in Hz (0-10000)
L125_R	air conduction 125 Hz (0-130)
L250_R	air 250 Hz
L500_R	air 500 Hz
L1000_R	air 1 kHz
L1500_R	air 1500 Hz
L2000_R	air 2 kHz
L3000_R	air 3000 Hz
L4000_R	air 4kHz
L6000_R	air 6000 Hz
L8000_R	air 8 kHz
FILNR_R	filenumber data
PROBE_R	probe type (v=adult k=child)
GAIN_R	gain in dB
STIM_R	stimulus 2=good 1=dub 0=bad
PEAK_R	stimulus peak in dB
STABIL_R	stimulus stability in %
NOISE_R	noise level in dB
PRCLOW_R	percentage low (under noise threshold)
ECHO_R	response echo in dB
REPRO_R	reproducibility in %
ARTF_R	artifact 0=not 1=maybe 2=certain
SPEC1_R	response 0 to 1 kHz (0=not 1=dub 2=+)
SPEC2_R	response 1 to 2 kHz (0=not 1=dub 2=+)
SPEC4_R	response 2 to 4 kHz (0=not 1=dub 2=+)
SPEC6_R	response 4 to 6 kHz (0=not 1=dub 2=+)
B250_R	bone conduction 250 Hz
B500_R	bone conduction 500 Hz
B1000_R	bone conduction 1 kHz
B1500_R	bone conduction 1500 Hz
B2000_R	bone conduction 2 kHz
B3000_R	bone conduction 3000 Hz
B4000_R	bone conduction 4 kHz
B6000_R	bone conduction 6000 Hz
B8000_R	bone conduction 8kHz
TYMP_R	tympanogramR 2=norm 1=under 0=flat
TYMP_L	tympanogramL 2=norm 1=under 0=flat

SUIS_L	tinnitus (j/n)
NIV_L	level of tinnitus dB (0-99)
FREQ_L	frequency tinnitus in Hz (0-10000)
L125_L	air 125 Hz (0-130)
L250_L	air 250 Hz
L500_L	air 500 Hz
L1000_L	air 1 kHz
L1500_L	air 1500 Hz
L2000_L	air 2 kHz
L3000_L	air 3000 Hz
L4000_L	air 4kHz
L6000_L	air 6000 Hz
L8000_L	air 8 kHz
B250_L	bone conduction 250 Hz
B500_L	bone conduction 500 Hz
B1000_L	bone conduction 1 kHz
B1500_L	bone conduction 1500 Hz
B2000_L	bone conduction 2 kHz
B3000_L	bone conduction 3000 Hz
B4000_L	bone conduction 4 kHz
B6000_L	bone conduction 6000 Hz
B8000_L	bone conduction 8kHz
FILNR_L	filenumber data
PROBE_R	probe type (v=adult k=child)
GAIN_R	gain in dB
STIM_R	stimulus 2=good 1=dub 0=bad
PEAK_L	stimulus peak in dB
STABIL_L	stimulus stability in %
NOISE_L	noise level in dB
PRCLOW_L	percentage low (under noise threshold)
ECHO_L	response echo in dB
REPRO_L	reproducibility in %
ARTF_L	artifact 0=no 1=maybe 2=certain
SPEC1_L	response 0 to 1 kHz (0=not 1=dub 2=+)
SPEC2_L	response 1 to 2 kHz (0=not 1=dub 2=+)
SPEC4_L	response 2 to 4 kHz (0=not 1=dub 2=+)
SPEC6_L	response 4 to 6 kHz (0=not 1=dub 2=+)
DIAG_R	diagnosis right ear
DIAG_L	diagnosis left ear

▸ 3 OTOACOUSTIC EMISSIONS IN NORMAL EARS

3.1 Introduction and review of the literature

The objective of this study was to obtain a standard of OAE measurement in normal hearing subjects, in other words: what level of OAEs is found in normal ears? This is important in order to adequately assess relationships between the pure tone audiometry thresholds and OAE patterns in cases of hearing loss (see Chapters 4 - 8). Of course, many parameters influence the otoacoustic emission response, but in an effort to untangle this complex matter, a clean set of basic data is needed.

The earliest reports on otoacoustic emissions in normal hearing ears (Kemp 1978, Wilson 1979, Wit and Ritsma 1979, Rutten 1980, Wit et al 1981, Johnsen and Elberling 1982) are difficult to compare because of the great variation in the equipment used, and the relatively small numbers of subjects studied. Besides, these authors usually concentrated on spontaneous otoacoustic emissions (Zurek 1981, Schloth 1983, Wier et al 1984, Köhler et al 1986), which appear in a varying percentage of normal ears only (see Chapter 1.4). However, after some years, a relative standardization of measurements occurred, which led to better comparable studies on TEOAEs in normal ears.

In their extensive 'field guide' to otoacoustic emission measurements, Kemp et al (1986) not only listed many practical do's and don'ts, but also presented the results of 130 ears, including 42 normal hearing ones. The nonlinear otoacoustic emission level between 1 and 2 kHz in response to click stimulation was found to decrease with increasing audiometric thresholds, with roughly a 10 dB loss in echo level for a 10 dB loss in hearing. About 5% of subjects with thresholds better than 15 dB HL produced no echo above the noise floor. The range of echo levels was almost 20 dB, with good individual reproducibility.

A comparison of different kinds of otoacoustic emissions in 28 normal ears was given by Probst et al (1986). Using their own, accurately described equipment, they found click-evoked otoacoustic emissions in all but one ear with average pure tone audiograms (PTA) better than 20 dB HL. There was a significant correlation between left and right ears for both frequency and amplitude parameters of click-evoked responses. Although the number of subjects in this study was rather small, the authors discerned three categories of emissions, based on the duration of the response and the absence or presence of spontaneous emissions.

Avan et al (1991) assessed detection thresholds of click evoked otoacoustic emissions in 44 right ears from normal hearing young adults with PTA better than 10 dB, and from ears with hearing loss. All normal ears showed otoacoustic emissions; in 85% the stimulation level at threshold was lowest between 780 - 1500 Hz. A statistically significant relationship was found between the otoacoustic emission threshold and all PTA thresholds ($p<0.001$), but also between all couples of PTA thresholds. Partial correlation analysis (stepwise regression) revealed that the best correlations existed between pure tone thresholds at 2 kHz and click response thresholds (nearly always close to 1 kHz). In their opinion this indicated that the otoacoustic emission threshold is not frequency specific.

Robinette (1992), reporting a study using the ILO88 system on 265 normals of all ages, also found emissions in 100% of ears, with rather liberal criteria. There was a decrease in emission response for right ears with age ($n=140$), and a statistically significant difference between male and female ears, the latter showing higher levels of emissions. At 3 and 4 kHz, otoacoustic emissions showed a statistically significant decrease with hearing thresholds up to 20 dB HL.

An even larger population of both normal and hearing impaired subjects was studied by LePage and Murray (1993), with respect to hearing levels at 1, 2 and 4 kHz and TEOAEs as measured by the ILO88 and ILO92 systems. They found a large variation in emission level for normal ears (the product of OAE level (ECHO) and reproducibility of the response ranged from +20 to -11), with some examples of absent emissions. Also, a decrease in otoacoustic emissions was found with increasing mean hearing thresholds for 1, 2 and 4 kHz, again with a 'large spread' not statistically defined.

Finally, Prieve et al (1993) reported the results from a group of 113 normal and hearing impaired ears, comparing worst thresholds at 0.5 to 4 kHz to broadband TEOAE responses. In a careful analysis using relative operator characteristics (ROC curves), they found that identification of hearing-impairment in ears was possible by 1, 2 and 4 kHz TEOAEs but not by 0.5 kHz responses. The information obtained from OAE level (ECHO) and reproducibility was highly redundant, and there was an abrupt decrease in incidence of TEOAEs above 20 dB hearing loss, especially at higher frequencies. Other studies concerning several aspects of otoacoustic emissions

in normal ears (e.g. newborns, aging effects) could be reviewed here, but this would not add significant material. However, it is worth noting that in some studies an early decrease of evoked OAE level with age has been suggested (Bonfils et al 1988, Collet et al 1989). This issue is dealt with in Chapter 5.

3.2 Subjects and methods

As the pure tone threshold in itself is a relative parameter, i.e. the relative threshold of hearing in comparison to thresholds of others, the definition of the control group is important. The inclusion criteria we used were as follows: no history of otologic disease or noise exposure, no present complaints of hearing or ear disease, normal eardrums on otoscopic examination, and age between 15 and 25 years. In all cases, a normal tympanogram was required as well. Even with these criteria, some variation in hearing threshold occurs in those with no complaints about their hearing at all. Excluded were those controls with a hearing loss of more than 15 dB at more than one frequency, or with a hearing loss exceeding 30 dB at any frequency.

Audiometric and otoacoustic emission data of 36 female and 25 male controls were collected as described in Chapter 2. In all cases, both ears were tested. Some subjects were tested in several sessions, to get an indication of the test-retest stability. Statistical analysis was performed using correlation/regression plots with special emphasis on the relation between mid-frequency hearing threshold and otoacoustic emission level. Also, differences between left and right ears were studied using two-tailed paired Student's t-tests. The differences between male and female ears were analyzed by two-tailed independent Student's t-tests. The combined effects of side and gender were subjected to multivariate analysis.

3.3 Results

It took approximately fifteen minutes per subject to perform a complete audio- and tympanogram, whereas the OAE measurement only took about three minutes (45 to 88 seconds per ear). The test-retest stability in terms of stimulus level, response pattern and level was good (variability $<=10\%$), though more quantifiable data on this aspect was not collected. The results of the audiometric and otoacoustic emission data analysis are summarized in Table 3.1.

TABLE 3.1 OTOACOUSTIC EMISSIONS AND HEARING IN NORMAL EARS

Audiometric and otoacoustic emission values for a group of control ears (normal hearing subjects), subdivided by side (R/L) and gender (F/M). From top to bottom are given: mid frequency average (MFA) hearing thresholds at 0.5, 1, 2 and 4 kHz in dB HL with standard deviations, mean otoacoustic emission response levels (OAE) in dB SPL with standard deviations, and median response reproducibility (REPRO) in percentages, with minimum and maximum values. The p-values denote the observed significance levels of the differences between these subgroups: the right column contains the values for the right/left comparisons ($p_{R,L}$), whereas the bottom lines show the significances ($p_{F,M}$) of the intergender differences. The main conclusion is that although females did not have significantly better hearing thresholds than males in this group, they did show higher emission levels.

MFA	R	L	total	$p_{R,L}$
all ears (n=122)	2.3±3.9	1.5±4.4	1.9±3.6	.134
female (n=36)	2.2±3.4	0.7±3.5	1.4±3.1	.005
male (n=25)	2.4±4.5	2.6±5.3	2.5±4.2	.886
$p_{F,M}$	.817	.142	.302	

OAE	R	L	total	$p_{R,L}$
all ears (n=122)	13.4±5.2	12.7±4.7	13.0±4.7	.072
female (n=36)	15.0±4.7	13.9±4.4	14.4±4.4	.017
male (n=25)	11.1±5.1	10.9±4.6	11.0±4.6	.843
$p_{F,M}$	.004	.018	.005	

REPRO	R	L	total
all ears (n=122)	94 (30-99)	93 (58-99)	92.5 (53-99)
female (n=36)	96 (78-99)	95 (64-99)	95 (71-99)
male (n=25)	91 (30-99)	90 (58-99)	89 (53-99)

3.3.1 Hearing thresholds

The mean air conduction threshold at 0.5, 1, 2 and 4 kHz (Mid Frequency Average or MFA) in individual cases varied from -6.25 to +13.75 dB HL with an average (geometric mean) of 1.9±3.6 dB HL. In the male subjects, mean MFA (for right and left ears together) was 2.5±4.2 dB HL and in females 1.4±3.1 dB HL. The mean absolute interaural difference in hearing level was 2.5±4.1 dB.

The only difference reaching statistical significance at two-tailed testing was the interaural difference in females, with their left ears being the better hearing ones ($p=.005$). However, in multivariate analysis this difference disappeared, meaning that the distribution of hearing thresholds across sides in females did not differ significantly from that in males. Also, it showed that the overall average hearing thresholds differed significantly from 0 dB HL.

3.3.2 Otoacoustic emissions

The pattern of the response spectrum is illustrated in Figure 3.1. There was a variation of about 10 dB over the major part of the frequency range. The largest amplitude of the response was found between 1 and 2 kHz, with a downsloping pattern towards higher frequencies. In the majority of ears, few emissions were found below 0.5 kHz or above 5 kHz. The microstructure of the pattern was quite unique in each subject and ear, and showed a good test-retest stability.

The input (click stimulus level) varied very little in this study, the mean peak level being 82±3.5 dB SPL. Regression analysis showed that only 9% of response variation could be explained by stimulus variation. Also, the noise level was acceptably low (34.4±0.2 dB SPL) in all cases. The mean values of the level of the OAE response (ECHO) are listed in the central part of Table 3.1. All ears showed otoacoustic emissions; the individual maximum and minimum levels were 25.5 (female right ear) and 1.9 (male left ear) dB SPL, respectively. There was no statistically significant difference in OAE level (ECHO) between left and right ears in the whole group (paired t-test, $p=.072$), though in the female ears such a difference was actually noted ($p=.017$). There was a marked influence of gender on the level of otoacoustic emissions: female ears compared favorably to male ears with regard to ECHO (independent t-test, in all cases $p<0.05$). Multivariate analysis confirmed the high significance of

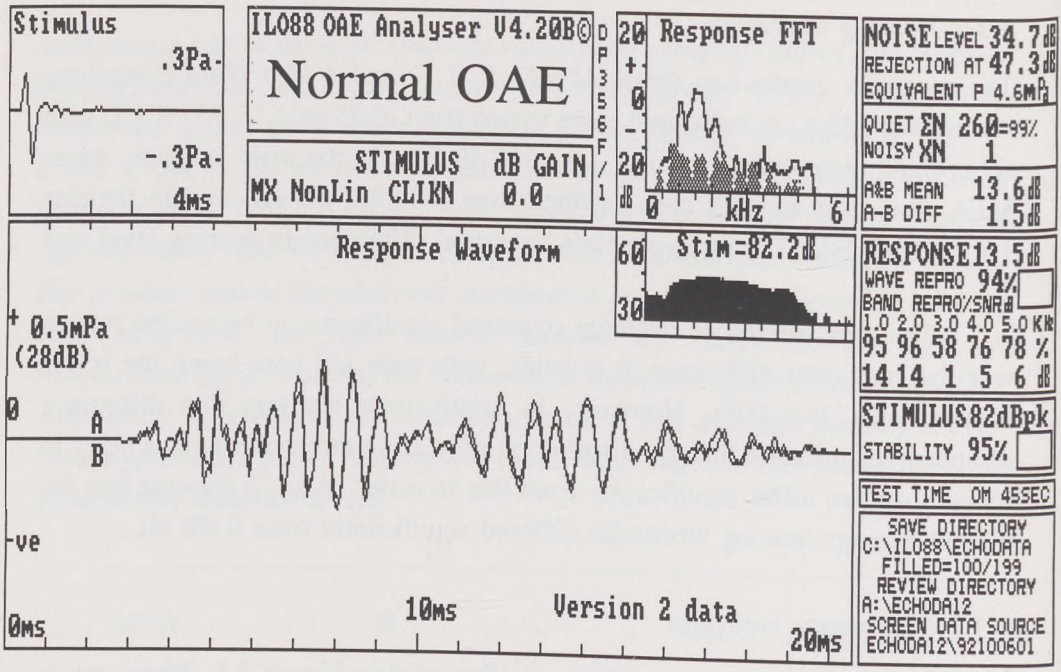


Figure 3.1

Example of otoacoustic emissions in a normal ear: high overall ECHO level (13.5 dB SPL) with a high reproducibility (REPRO 94%). Note the typical downsloping pattern of the response spectrum with a maximum amplitude between 1 and 2 kHz.

these results. Due to the non-normality of the distribution of the REPRO values, a multivariate analysis of this parameter could not be performed. Consequently, median values are given in Table 3.1 (bottom part), together with minimum and maximum values. Due to software limitations, the highest reproducibility value registered was 99% instead of 100%.

3.3.3 Correlation between hearing thresholds and OAE levels

Regression statistics were calculated for otoacoustic emission levels on hearing thresholds, for right and left ears separately. A visual representation of the results for the otoacoustic emission level (ECHO) is given in Figure 3.2. The reproducibility of the response (REPRO) is plotted in Figure 3.3. There is a correlation between mid frequency average hearing threshold (MFA) and OAE level (ECHO) of -0.46 with a very high significance ($p=0.0002$) for both right

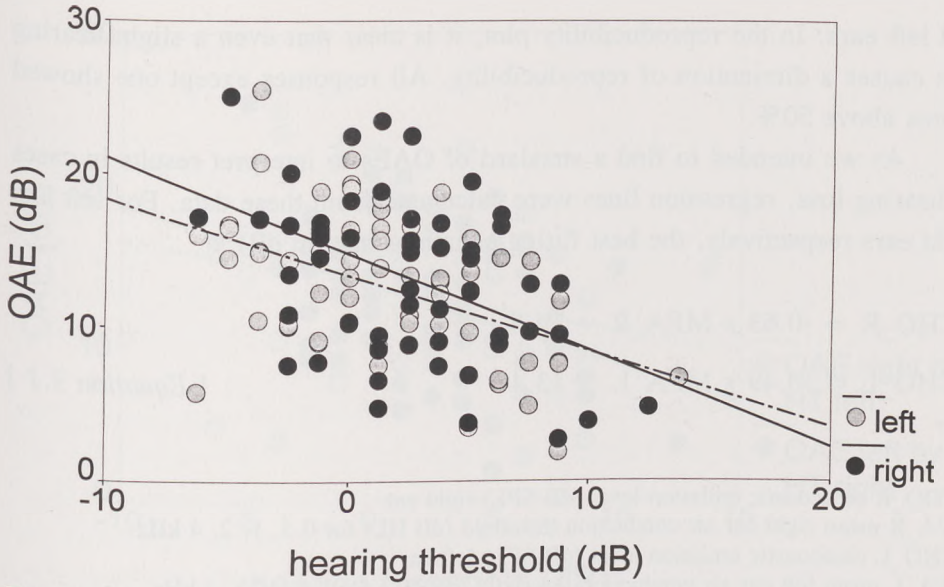


Figure 3.2

Correlation between otoacoustic emission level (ECHO in dB SPL) and pure tone threshold (MFA in dB HL) in 61 right and left ears of control group. There is a statistically significant negative correlation for both sides ($r=-0.46$, $p<0.001$), meaning that even a slight hearing loss results in smaller otoacoustic emissions.

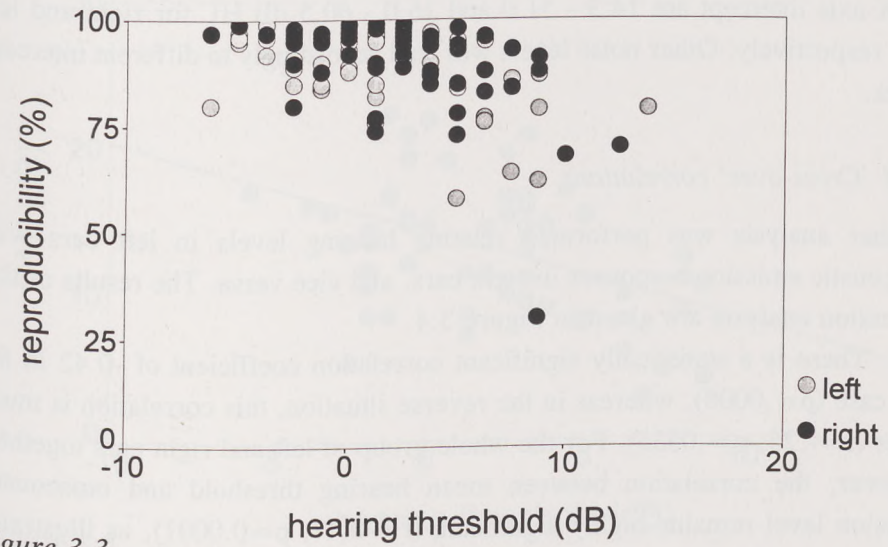


Figure 3.3

Relation between reproducibility of the response (REPRO in %) and pure tone threshold (MFA in dB HL) in 122 control ears, showing larger variability (lower reproducibility) in ears with even slight deterioration of hearing. The values are not normally distributed.

and left ears. In the reproducibility plot, it is clear that even a slight hearing loss causes a diminution of reproducibility. All responses except one showed scores above 50%.

As we intended to find a standard of OAEs to interpret results in cases of hearing loss, regression lines were calculated from these data. For left and right ears respectively, the best fitting equations are (in dB):

$$ECHO\_R = -0.63 \times MFA\_R + 14.8$$

$$ECHO\_L = -0.49 \times MFA\_L + 13.4 \qquad [\textit{ Equation 3.1 }]$$

ECHO_R otoacoustic emission level (dB SPL) right ear
MFA_R mean right ear air conduction threshold (dB HL) for 0.5, 1, 2, 4 kHz
ECHO_L otoacoustic emission level (dB SPL) left ear
MFA_L mean left ear air conduction threshold (dB HL) for 0.5, 1, 2, 4 kHz

If the noise floor is assumed to be 0 dB SPL on average, this means the OAEs will disappear when the hearing threshold (MFA) exceeds approximately 25 dB HL (23.6 and 27.2 dB for R/L ears). The 95% confidence intervals of this X-axis intercept are 14.3 - 51.0 and 16.0 - 60.5 dB HL for right and left ears, respectively. Other noise levels will lead accordingly to different intercept values.

3.3.4 'Cross-over' correlations

Another analysis was performed relating hearing levels in left ears with otoacoustic emission responses in right ears, and vice versa. The results of this regression analysis are given in Figure 3.4.

There is a statistically significant correlation coefficient of -0.42 in the first case ($p=.0008$), whereas in the reverse situation, this correlation is much lower ($r=-.25$, $p=.0535$). For the whole group of left and right ears together, however, the correlation between mean hearing threshold and otoacoustic emission level remains highly significant ($r=-0.47$, $p=0.0001$), as illustrated in Figure 3.5. In this plot, left and right ear values are averaged for each individual case.

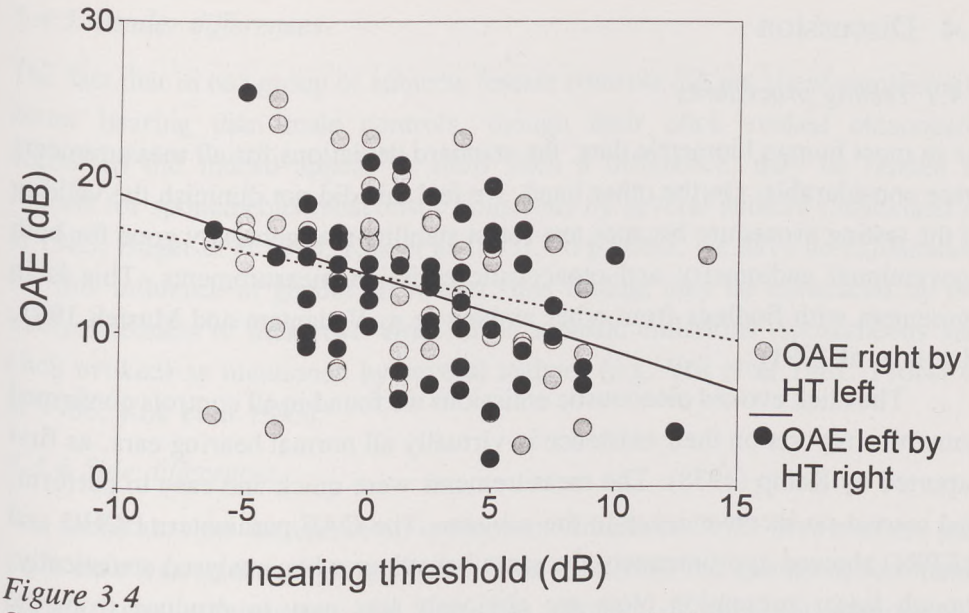


Figure 3.4
Cross-over interaural relationships between OAE levels (dB SPL) and pure tone thresholds (MFA in dB HL). Left ear echoes correlate better with right ear hearing than do right ear echoes with left ear hearing (r=-0.42 and -0.25, respectively). This asymmetry may be due to central (efferent) influences on otoacoustic emissions.

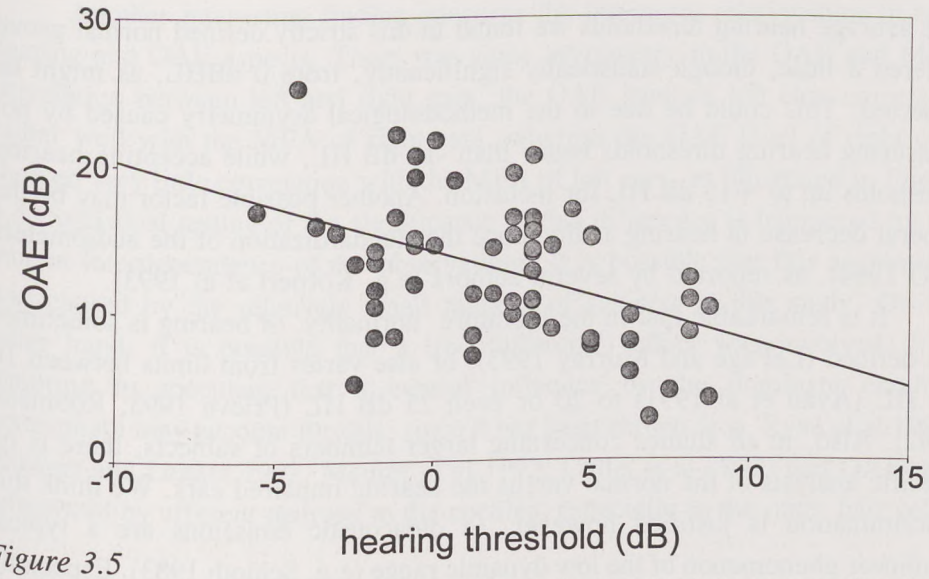


Figure 3.5
Overall correlation of otoacoustic emissions with hearing thresholds in a group of controls. In each case, the geometric mean of right and left ear ECHO (dB SPL) and MFA (dB HL) are calculated. The negative correlation (r=-0.47) is highly significant (p=.0001), though there is obvious scatter in the data.

3.4 Discussion

3.4.1 Testing procedures

As in most human biometric data, the standard deviations for all measurements were considerable. On the other hand, we feel this did not diminish the validity of the testing procedure because test-retest stability was generally good for both conventional audiometry and otoacoustic emission measurements. This is in agreement with findings from other authors (e.g. Vedantam and Musiek 1991, Harris et al 1991).

The click evoked otoacoustic emissions we found in all controls confirmed numerous reports on their existence in virtually all normal hearing ears, as first reported by Kemp (1978). The measurements were quick and easy to perform, and caused no inconvenience to the subjects. The OAE parameters ECHO and REPRO showed approximately the same behaviour when analysed statistically, though linear regression plots are obviously less easy to produce from the REPRO values.

3.4.2 Hearing thresholds

The average hearing thresholds we found in this strictly defined normal group differed a little, though statistically significantly, from 0 dBHL, as might be expected. This could be due to the methodological asymmetry caused by not measuring hearing thresholds better than -10 dB HL, while accepting hearing thresholds up to +15 dB HL for inclusion. Another possible factor may be the general decrease in hearing acuity since the standardization of the audiometers (ISO 1964), as reported by several authors (e.g. Körpert et al 1993).

It is remarkable that in the literature 'normality' of hearing is sometimes not defined (LePage and Murray 1993), or else varies from limits between 10 dB HL (Avan et al 1991) to 20 or even 25 dB HL (Prieve 1993, Robinette 1992). Also, in all studies concerning larger numbers of subjects, there is no specific analysis of the normal versus the hearing impaired ears. We think this discrimination is justified however, as otoacoustic emissions are a typical nonlinear phenomenon of the low dynamic range (e.g. Schloth 1983). Especially in view of the relations with audiometric thresholds as subjective parameters of auditory function, careful analysis of normative data is mandatory.

3.4.3 Gender differences

The fact that in our group of subjects female controls did not show significantly better hearing than male controls, though their click evoked otoacoustic emissions did indeed appear to show such a difference, may be related to reports for spontaneous otoacoustic emissions by several authors (Strickland et al 1985, Bilger et al 1990, Kok et al 1993). At present, we have no explanation for this influence of gender. However, this finding may be influenced by the interrelatedness of these two kinds of otoacoustic emissions (spontaneous and click evoked) as mentioned by several authors (e.g. Wit et al 1981, Probst et al 1986, Kok et al 1993).

3.4.4 Side differences

We found that the difference in otoacoustic emissions level between left and right ears was statistically significant. This confirmed the results of Robinette (1992), who unfortunately did not state number of ears nor audiometric thresholds in his analysis. The fact that no such difference was found by Probst et al (1986) may have been due to the small number of subjects analysed in their study, and the somewhat different parameters they used.

Another interesting finding concerns the interaural relationships in both hearing and OAE aspects. There was some asymmetry in the OAE and MFA correlation between left and right ears: the OAE level of left ears correlated rather well with the MFA of right ears, whereas the OAE level of right ears showed very little correlation with the MFA of left ears, as illustrated in Figure 3.5. Statistical testing of the significance of this difference is hampered by the mutual interdependence of the observations. It is possible that this asymmetry was caused by the relatively small number of subjects in this study. On the other hand, it is possible that a true (efferent?) effect was involved. It is tempting to speculate that a central influence by the dominant cerebral hemisphere may account for this, since it has been shown (e.g. Ryan et al 1991, Plinkert and Lenarz 1992, Maurer et al 1992, Collet et al 1992) that OAEs are influenced by efferent neurons to the cochlea, especially to the outer hair cells.

3.4.5 Relation between hearing thresholds and OAEs

One of the most surprising results of this study is the finding that even in a strictly defined group of normal hearing subjects, there is a statistically

significant correlation between hearing 'loss' and otoacoustic emission level, as shown in Figure 3.2. Thus, it seems possible to extrapolate data from a group of normal hearing ears to ears with hearing loss. Consequently, the finding that OAEs rarely occur above 25-30 dB hearing loss may also be deduced from ears with no hearing loss at all.

Nonetheless, we are well aware of the fact that these findings only apply to groups of subjects, and that it is not possible to make definite statements in individual cases. However, this finding makes it possible to screen (adult) populations for subclinical hearing deterioration in a very rapid and objective way. Thus, to paraphrase Kemp et al (1986), otoacoustic emissions may not quantify hearing loss, but be helpful in predicting its development. It is surprising, that in their study some 5% of subjects with hearing thresholds better than 15 dB HL did not show otoacoustic emissions: this may be due to high noise levels or other technical impediments. The setting seems comparable to our study however, because they also presented 'first take' data, obtained under non ideal conditions (i.e. not in the laboratory).

The data from Avan et al (1991) also showed interesting correlations between otoacoustic emissions and hearing thresholds: these concerned detection thresholds however, not otoacoustic emission levels for a certain stimulus level. A problem arose thus when there were no emissions at all: the 'detection level' was set at 40 dB HL. We feel that this may seriously interfere with any statistical analysis performed, and that the correlations thus computed should be very cautiously interpreted.

In contrast to our study, LePage and Murray (1993), using the same equipment, found a relatively high number of absent emissions for normals. Percentages were not stated, but appeared to be around 5-10%, as there were 15% of ears with hearing thresholds better than 30 dB HL which did not show emissions. This difference may be due to measuring conditions or subject selection. Their graphs showed nonlinear correlations between hearing levels and otoacoustic emission levels, probably because the product of ECHO and REPRO was plotted, and many subjects with hearing loss were included.

The results of Prieve et al (1993), though presented in a different way, were confirmed by our study. Moreover, we found it possible not only to differentiate between normality or non-normality of hearing by means of otoacoustic emission measurement, but also to quantify this relationship in a

linear equation. The absence of otoacoustic emissions Prieve et al found at thresholds above approximately 20 dB HL is well explained by this equation.

3.4.6 Clinical relevance

One of the most difficult, though important, issues to be dealt with is the question whether the statistically significant findings from this study have any clinical relevance. As the latter is not computable, a definite answer is hard to give. The slightly higher click-evoked otoacoustic emission levels in female ears may be of interest to explain earlier reported data on spontaneous emissions, but this seems not a clinically relevant issue.

It is important however, that for a group of subjects it seems possible to detect hearing deterioration in a quick and objective manner, even before complaints arise. Many adults nowadays are being screened by pure tone audiometry for potential hearing loss due to occupational noise exposure. There are also indications that there is a general decline in hearing acuity in school children and young adults (e.g. Körpert et al 1993).

The current screening procedures often perform poorly in strict cost benefit terms (McBride and Calvert 1994), and could be improved by implementing otoacoustic emission measurements. This appears to be highly relevant, especially in view of the social and medicolegal consequences of established hearing loss.

3.5 Conclusions

Otoacoustic emission measurements were easily performed in normal hearing adults. Although there was considerable interindividual and interaural variation in OAE level (and reproducibility), statistically significant correlations between hearing thresholds and otoacoustic emission levels were found in strictly defined groups of normal hearing subjects. Regression analysis of these data can explain the presence or absence of otoacoustic emissions in ears with hearing loss. Moreover, this seems to open up possibilities for effective screening of children and adults.

References

Avan P, Bonfils P, Loth D, Narcy P, Trotoux J (1991): Quantitative assessment of human cochlear function by evoked otoacoustic emissions. Hear Res 52:99-112

Bilger RC, Matthies ML, Hammel DR, Demorest ME (1990): Genetic implications of gender differences in the prevalence of spontaneous otoacoustic emissions. J Speech Hear Res 33:418-432

Bonfils P, Bertrand Y, Uziel A (1988): Evoked otoacoustic emissions: normative data and presbycusis. Audiology 27:27-35

Collet L, Disant F, Morgon A (1989): Effet de l'âge sur les otoémissions acoustiques. Rev Laryngol Otol Rhinol 110:67-68

Collet L, Veuillet E, Bene J, Morgon A (1992): Effects of contralateral white noise on click-evoked emissions in normal and sensorineural ears: towards an exploration of the medial olivocochlear system. Audiology 31:1-7

Harris FP, Probst R, Wenger R (1991): Repeatability of transiently evoked otoacoustic emissions in normally hearing humans. Audiology 30:135-141

Johnsen NJ, Elberling C (1982): Evoked acoustic emissions from the human ear I. Equipment and response parameters. Scand Audiol 11:3-12

Kemp DT (1978): Stimulated emissions from within the human auditory system. J Acoust Soc Am 64(5):1386-1391

Kemp DT, Bray P, Alexander L, Brown AM (1986): Acoustic emission cochleography-practical aspects. Scand Audiol Suppl 25:71-95

Köhler W, Fredriksen E, Fritze W (1986): Spontaneous otoacoustic emissions--a comparison of the left versus the right ear. Arch Otorhinolaryngol 243:43-46

Kok MR, Zanten GA van, Brocaar MP (1993): Aspects of spontaneous oto-acoustic emissions in healthy newborns. Hear Res 69:115-123

Körpert K, Miksch P, Winker N (1993): Einfluss von Berufs- und Freizeitlärm bei Schülern und Lehrlingen. In: Stress am Arbeitsplatz. Epidemiologische Erhebungen und ihre Bewertung:130-135. Allgemeine Unfallversicherungsanstalt, Wien.

LePage EL, Murray NM (1993): Click-evoked otoacoustic emissions: comparing emission strengths with pure tone audiometric thresholds. Austr J Audiol 15:9-22

Maurer J, Beck A, Mann W, Mintert R (1992): Veränderungen otoakustischer Emissionen unter gleichzeitiger Beschallung des Gegenohres bei Normalpersonen und Patienten mit einseitigem Akustikusneurinom. Laryngorhinootologie 71:69-73

McBride D, Calvert I (1994): Audiometry in Industry. Ann Occup Hyg 38(2):219-230

Plinkert PK, Lenarz T (1992): Evozierte otoakustische Emissionen und ihre Beeinflussung durch kontralaterale akustische Stimulation. Laryngorhinootologie 71:74-78

Prieve BA, Gorga MP, Schmidt A, Neely S, Peters J, Schultes L, Jestaedt W (1993): Analysis of transient-evoked otoacoustic emissions in normal-hearing and hearing-impaired ears. J Acoust Soc Am 93(6):3308-3319

Probst R, Coats AC, Martin GK, Lonsbury Martin BL (1986): Spontaneous, click-, and toneburst-evoked otoacoustic emissions from normal ears. Hear Res 21:261-275

Robinette MS (1992): Clinical observations with transient evoked otoacoustic emissions with adults. Semin Hear 13:23-35

Rutten WLC (1980): Evoked acoustic emissions from within normal and abnormal human ears: comparison with audiometric and electrocochleographic findings. Hear Res 2:263-271

Ryan S, Kemp DT, Hinchcliffe R (1991): The influence of contralateral acoustic stimulation

on click- evoked otoacoustic emissions in humans. Br J Audiol 25:391-397
Schloth E (1983): Relation between spectral composition of spontaneous otoacoustic emissions and fine-structure of threshold in quiet. Acustica 53:250-256
Strickland EA, Burns EM, Tubis A (1985): Incidence of spontaneous otoacoustic emissions in children and infants. J Acoust Soc Am 78:931-935
Vedantam R, Musiek FE (1991): Click evoked otoacoustic emissions in adult subjects: standard indices and test-retest reliability. Am J Otol 12:435-442
Wier CC, Norton SJ, Kincaid GE (1984): Spontaneous narrow band otoacoustic signals emitted by human ears: a replication. J Acoust Soc Am 76(4):1248-1250
Wilson JP (1979): Recording of the Kemp echo and tinnitus from the ear canal without averaging. Proc Physiol Soc 19(2):8-9
Wit HP, Ritsma RJ (1979): Stimulated acoustic emissions from the human ear. J Acoust Soc Am 66(3):911-913
Wit HP, Langevoort JC, Ritsma RJ (1981): Frequency spectra of cochlear acoustic emissions ("Kemp-echoes"). J Acoust Soc Am 70(2):437-445
Zurek PM (1981): Spontaneous narrow-band acoustic signals emitted by human ears. J Acoust Soc Am 69:514-523

▸ 4 INFLUENCE OF MIDDLE EAR FUNCTION ON OTOACOUSTIC EMISSIONS

4.1 Introduction

It is well known that the measurement of otoacoustic emissions is influenced by the status of the external ear canal and the function of the middle ear. Diseases of the middle ear are common and form a major cause of hearing impairment: in our patient population of mainly adults it was the main contributing factor in 15% of the ears. In children, the incidence is even higher (e.g. Zielhuis et al 1990, Schilder 1993). Besides, it can be theoretically argumented that evoked OAEs may be heavily influenced by middle ear dysfunction: both the stimulus and the response are hampered on their way. This may not only cause a decreased stimulation of OHCs in the cochlea, but also a diminished transfer of acoustic energy back into the external ear canal (e.g. Bray 1989). In purely cochlear dysfunction no such double impediment exists. Therefore, it is necessary to examine this aspect in more detail.

Anatomically seen, the middle ear, consisting of the tympanic membrane and the ossicles with the air-filled space around them, forms the gateway from the ear canal to the cochlea. Its mechanical properties were extensively studied by many authors (e.g. Helmholtz 1863, Békésy 1939). From a functional point of view, the condition of middle ear disease may be considered as one of diminished impedance matching between external ear (air) and inner ear (perilymphatic fluid), causing a loss of (acoustic) energy transfer to the cochlea, which results in poor hearing.

It is important to realise that the real magnitude of impedance mismatch is difficult to assess: it may only indirectly be calculated from the difference between air and bone conduction thresholds. As the bone conduction threshold is influenced by the external and middle ear condition, it is not an accurate indicator of perception threshold (sensorineural loss) and may not be regarded as the actual sensorineural threshold (Huizing 1960). The perception threshold, nevertheless, is the parameter most closely linked to cochlear 'threshold' or function.

Another indirect way to assess middle ear integrity is by impedance (oto-admittance) measurement, also called tympanometry. Usually, in the clinical setting a 220 Hz tone is employed to evaluate the amount of acoustic energy reflected by the middle ear system, thus yielding information on its compliance ('elasticity'). Its graphic representation, the tympanogram, shows middle ear

compliance as a function of ear canal pressure. However, this method is not suitable to quantify the extent of the modification of the transfer function of the middle ear at the higher frequencies where otoacoustic emissions are usually found (>0.5 kHz).

The subject of otoacoustic emissions in ears with conductive hearing losses is dealt with by several authors. Surprisingly, however, there are hardly any data on adults, the main part concerning children and infants. In an experimental setting, Wilson (1980) found changes in tone-burst induced acoustic responses under influence of middle ear pressure changes. These changes were larger than the concomitant changes in fine-structure of the audiogram, which he attributed to the inward and outward passage through the middle ear of both stimulus and response. In their study of 50 ears with hearing loss, Probst et al (1987) simply left out conductive losses, as these were not expected to show otoacoustic emissions at all.

A few nice experimental data were given by Bray (1989). In one normal hearing ear, he studied the effect on otoacoustic emissions of middle ear pressure changes and loading the tympanic membrane with droplets of water. This resulted in an amplitude decrease for the lower frequencies, whereas the high frequency OAEs remained relatively unaffected. The loss of emission intensity (in dB) was reported as being approximately twice the subjective threshold shift. Kemp et al (1990) also found a reduction of emission energy below 2 kHz in middle ear impairment, but a possible enhancement for high frequencies (>3 kHz) in one adult ear. They further state that "..there is no doubt that middle ear fluid will prevent the reception of otoacoustic emissions".

This was supported by work from Lamprecht (1991), who found few emissions in 37 ears of all ages with middle ear dysfunction. Although no hearing thresholds are given, it may be inferred that minor impediments (perforated tympanic membrane, partial obstruction with fluid) will allow some emissions to emerge. A large study in children (266 ears) was reported by Erwig et al (1991), who found emissions in only 12% of ears with a flat tympanogram. They failed to obtain emissions from ears with thresholds above 20 dB HL. Even slight middle ear underpressure (as shown by the tympanogram) reduced the rate of recorded otoacoustic emissions, compared to normal ears.

Prieve (1992) supposed that differences in otoacoustic emission level

between infants and adults may be due to differences in ear canal volume and middle ear impedance. This could enhance infants' OAEs by efficient energy transfer to the (high impedance) microphone of the measurement system. In a graph of 6 ears of children with middle ear disease, a negative effect on otoacoustic emissions is shown, depending on the magnitude of the air/bone gap. Owens et al (1992) discussed the implications of middle ear disease for infant screening by OAEs, but did not give data. In a study of 41 neonates, Chang et al (1993) found diminished otoacoustic emissions in seven ears with middle ear abnormalities, though the majority improved with retesting after one month. Also, they stressed the importance of a clear, non-collapsed ear canal for obtaining otoacoustic emission responses in this population.

Another study on this subject was performed by Kok, who measured otoacoustic emissions in a large number of healthy newborns and at risk infants (Kok 1994). The data presented suggest that the growth of the otoacoustic emission response in the first few days post partum is due to the middle ear clearance of amniotic fluid. This underscores the importance of intact middle ear function for otoacoustic emission measurements, with implications for infant screening.

In summary, although most authors agree that an intact middle ear is important for the adequate reception of otoacoustic emissions, it appears that there is still a lack of data on otoacoustic emissions in adult ears with middle ear impairment. Furthermore, there is no proof of the supposedly two-fold influence of the middle ear on otoacoustic emissions.

From this theoretically expected two-fold dependence of otoacoustic emissions on the middle ear (Wilson 1980, Bray 1989) the question arises if an ear with a certain conductive loss and intact cochlea shows more or less emissions than an ear with a similar but purely sensorineural loss and a perfect middle ear. In a group of hearing impaired ears it would be expected that high otoacoustic emission levels correlate with a relatively good middle ear function. There are some considerations to be made concerning the comparison of sensorineural to conductive hearing loss in a group of patients and, similarly, concerning the otoacoustic emissions measurements involved.

Firstly, the maximum hearing loss in complete absence of middle ear function (e.g. after radical mastoidectomy) is 50-60 dB, caused by lack of impedance matching and phase shift between oval and round window.

Sensorineural hearing loss may be as severe as 120-130 dB. Otoacoustic emissions are virtually never found in ears with average thresholds over 40 dB HL (e.g. Kemp et al 1986, Probst et al 1987), so only part of the range of losses may be evaluated. Secondly, the frequencies involved are not completely overlapping: whereas SNHL may occur in any frequency region, it usually is most prominent in the higher frequencies (see Chapter 4.3 and Figure 4.1). Conductive hearing losses however, tend to be larger in the lower frequency range, where the impedance matching is most vulnerable due to the resonant properties of the middle ear. Thirdly, as explained above, the precise proportion of these two kinds of hearing impairment in one ear is difficult to assess, and finally, there are many different diseases involved which may differ in their influence on both middle and inner ear.

From a theoretical point of view, the question is whether the difference between source and transmission degeneration (one-to-X relation versus one-to-one relation) may be assessed by evoked OAE measurement (nonlinear input/output function). A decrease of 20 dB in stimulus intensity by middle ear pathology may constitute a relatively small effect in comparison to the (much weaker) emission having to struggle its way out through the same middle ear. Another aspect concerns the spontaneous emissions which may be triggered by low level external stimuli: they may corroborate the evoked emissions if synchronized. On the other hand, if this triggering fails, they may act as background noise obscuring the evoked otoacoustic emissions.

4.2 Subjects and methods

Ideally, the hypothesis of the double impact of the middle ear on otoacoustic emissions should be tested by experimentally inducing varying degrees of conductive hearing loss in a sufficiently large number of patients, and subsequently inducing similar sensorineural hearing losses in the same. If there would be more emissions in the last case, the hypothesis could be considered proven. However, as this experiment is obviously not possible, we will analyze the data we obtained according to the methods described before (Chapter 2).

In our population of 500 subjects, a significant number suffered from different kinds of SNHL, often with at least some degree of middle ear impairment. Besides, in about 15%, a predominantly conductive hearing loss was present. As already mentioned in Chapter 2, in some ears with a very good

air conduction threshold (MFA <10 dB HL), no bone conduction was measured. We therefore left out patients with very small (<15 dB) conductive hearing losses, as this group may not be representative. Also, very large hearing losses (>40 dB) were left out, as these may distort the picture on the other side of the scale. The dynamic range we investigated ran from 15 to 40 dB total hearing loss, divided into 5 dB classes (15-19 dB, 20-24 dB etc).

The frequency range studied was limited from 0.5 to 4 kHz, leaving out 0.25 and 8 kHz for reasons mentioned above. Thus, instead of the ideal data pool of ears with either a purely conductive or a purely sensorineural hearing loss for a certain frequency, the groups in this study consisted of varying numbers of ears with varying degrees of mixed hearing losses. For example, all ears with a total hearing loss of 30 dB at 2 kHz form a mixture, ranging from ears with a purely conductive loss of 30 dB (and no sensorineural loss) to ears with a purely sensorineural loss of 30 dB (with no conductive component at all). Similar groups may be formed by all ears with a total loss of 15 dB at 4 kHz, 40 dB at 2 kHz, etc. Regression analysis was performed and partial correlation coefficients were calculated between the otoacoustic emission level (ECHO), air conduction and bone conduction thresholds.

For a group of ears with a given total hearing loss, but with a varying degree of sensorineural and conductive components (at a certain frequency), the correlation between otoacoustic emission level (ECHO) and bone conduction threshold was studied. If this correlation should prove to be positive, the influence of the middle ear on the OAE is stronger than that of the inner ear. In case of a negative correlation, it implies that the influence of the inner ear on otoacoustic emissions is stronger than that of the middle ear.

To check for counteracting effects between different frequencies due to possible frequency dependencies, a similar analysis was performed with semiquantitative data. Accordingly, data on hearing thresholds at one single frequency rather than 'overall' thresholds were considered for detailed analysis. The visually scored otoacoustic emission response in a certain frequency region was related to the bone conduction hearing loss at 1, 2 or 4 kHz, for a given total hearing loss. (The procedure of visual scoring is described in Chapter 2.3.3.) In this way, we tried to obtain more frequency specific correlations between otoacoustic emissions and hearing than by taking into account only the overall OAE level.

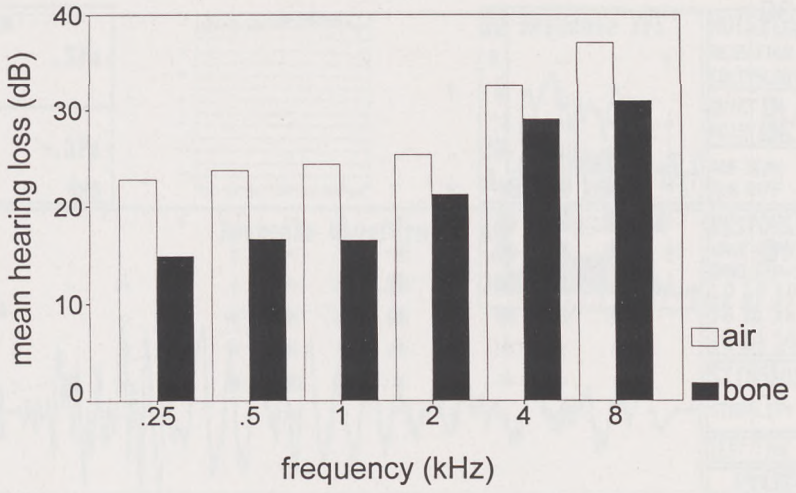


Figure 4.1
Mean hearing loss (dB) as a function of frequency (kHz) in hearing impaired but not deaf ears. The number of ears ranged from 718 to 968. In the higher frequencies the mean total hearing losses are larger, but the conductive component (air-bone gap) is relatively smaller.

4.3 Results

In total, the results obtained in over 500 ears were analysed, resulting in adequate group sizes per frequency and dynamic range (31 - 88 ears per group). This seemed an appropriate number for a balanced analysis. Evidently, the smaller the population, the more likely the appearance of 'pseudo-correlations', whereas the larger the population, the higher the risk of data contamination by other factors (Van Houwelingen et al 1995).

Determining the amount of conductive versus sensorineural hearing loss across frequencies, we found that the former is more prominent in the lower, the latter in the higher frequencies, as displayed in Figure 4.1. Although the standard deviations were considerable, the general trend was a decrease of the air-bone gap with increasing frequency. In Figure 4.2 the average midfrequency hearing loss (air and bone conduction together at 0.5, 1, 2 and 4 kHz) in all ears of the study population (n=952) was related to the level of the otoacoustic emissions. Notwithstanding the scatter of data, there was a negative correlation with a high significance, as could be expected. It should be observed that this plot is meant to give an overview of the data, which is not corrected for several confounding factors like diagnosis (psychogenic loss), stimulus variability, etc.

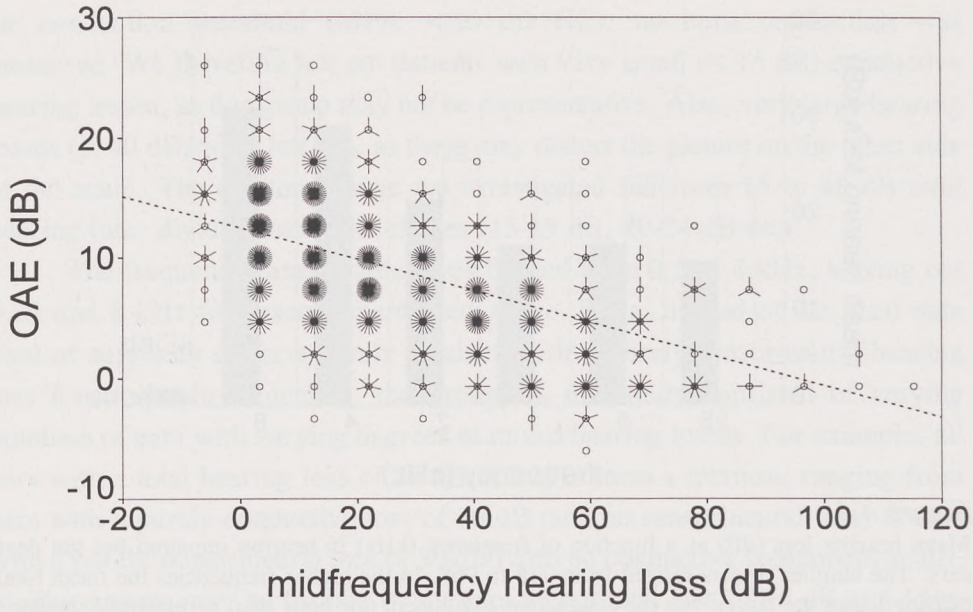


Figure 4.2
Relation between OAE level (dB SPL) and midfrequency average loss (MFA in dB) in 964 ears: the larger the (total) hearing loss, the lower the level of the otoacoustic emissions. There is a negative correlation ($r=-.58$) with a high significance ($p<0.00005$).

Extreme examples of high emissions are given in Figure 4.3.Only a very small percentage of the ears showed either purely conductive or purely sensorineural hearing loss. In 46 cases (including 14 deaf ears) a purely sensorineural loss was measured (65.8 ± 48 dB), with a mean otoacoustic emission level of 6.5 ± 4.8 dB SPL. Only 13 ears showed a purely conductive hearing loss (mean 16.5 ± 15 dB) with mean otoacoustic emission levels of 12.9 ± 6.5 dB SPL.

In all ears where bone conduction was measured (and excluding deaf ears), the relation between bone conduction (sensorineural) and air conduction (conductive) threshold at 1 kHz was investigated, as shown in Figure 4.4. There appeared to be virtually no correlation between these parameters. This means that any amount of middle ear dysfunction may coincide with any level of inner ear dysfunction. This plot could be considered as a composition of ears with mixed hearing losses, with the exception of those ears that lie on the X- or Y-axis: these have purely sensorineural or conductive losses.

The stratification for total hearing losses as described in the previous paragraph could be imagined as a diagonal gridding of this plot: for example by

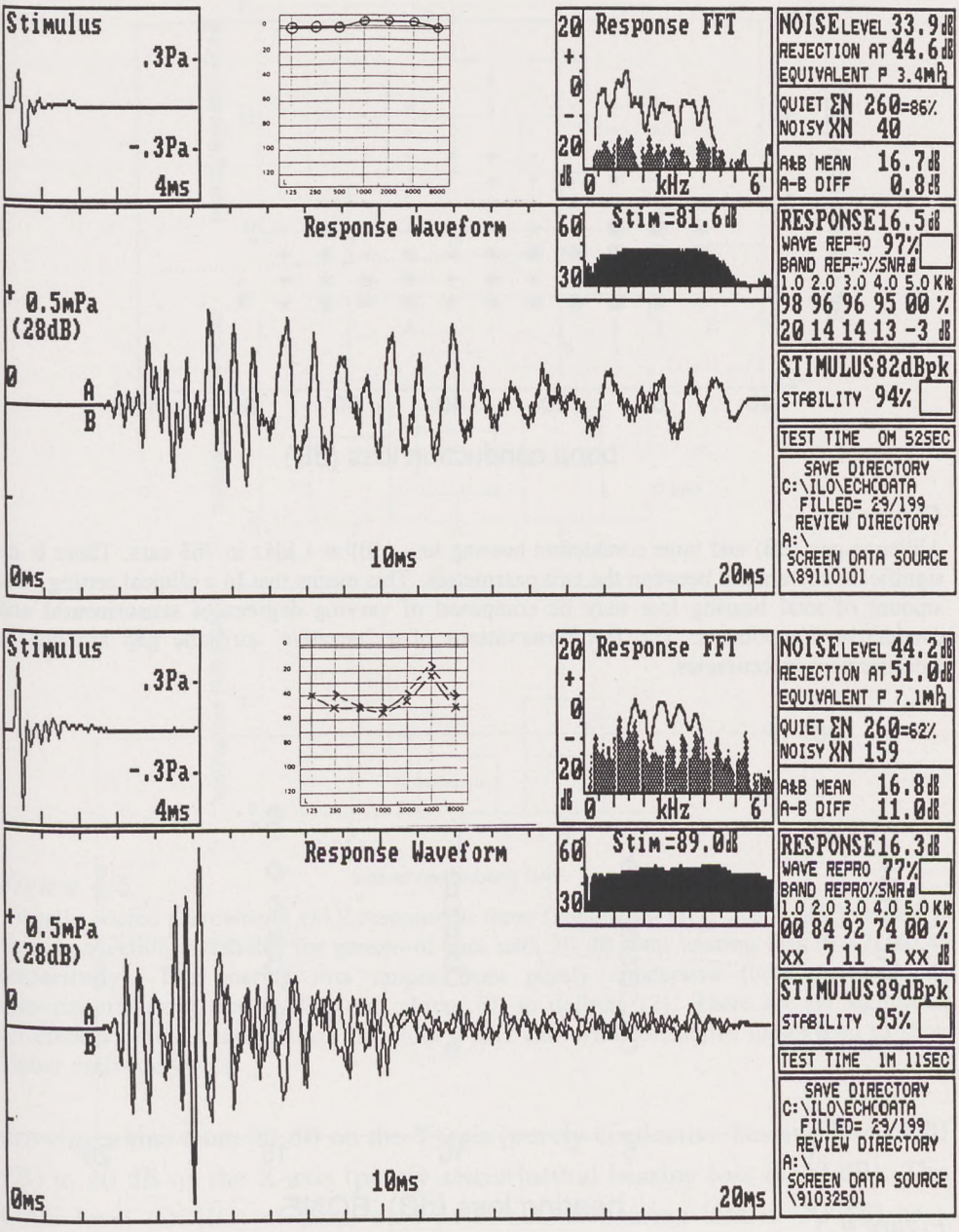


Figure 4.3
Examples of high otoacoustic emission levels in case of good hearing (A, above) or poor hearing (B, below). The audiograms are inserted between stimulus and response window. In case B, the hearing is relatively good in the high frequencies, and the stimulus level is (too) high. This gives rise to an apparently normal otoacoustic emission response and scatter of data as in Figure 4.2.

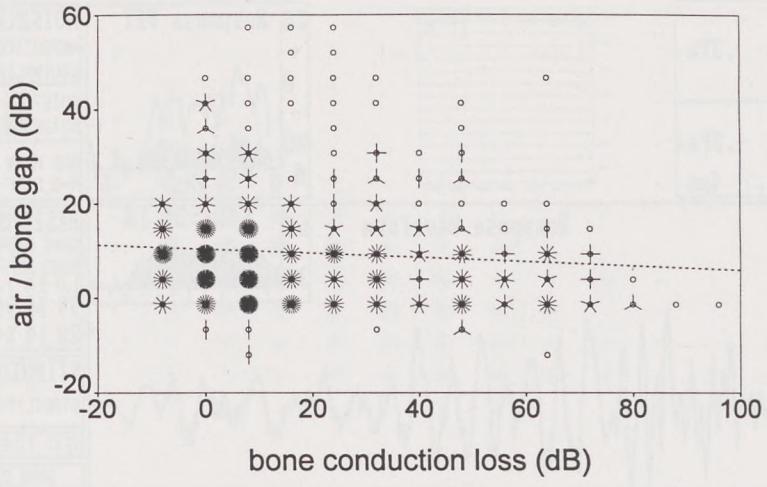


Figure 4.4
Air/bone gap (dB) and bone conduction hearing loss (dB) at 1 kHz in 763 ears. There is no significant correlation between the two parameters. This means that in a clinical setting, any amount of total hearing loss may be composed of varying degrees of sensorineural and conductive components. The few observations of a 'negative' air/bone gap are due to measurement inaccuracies.

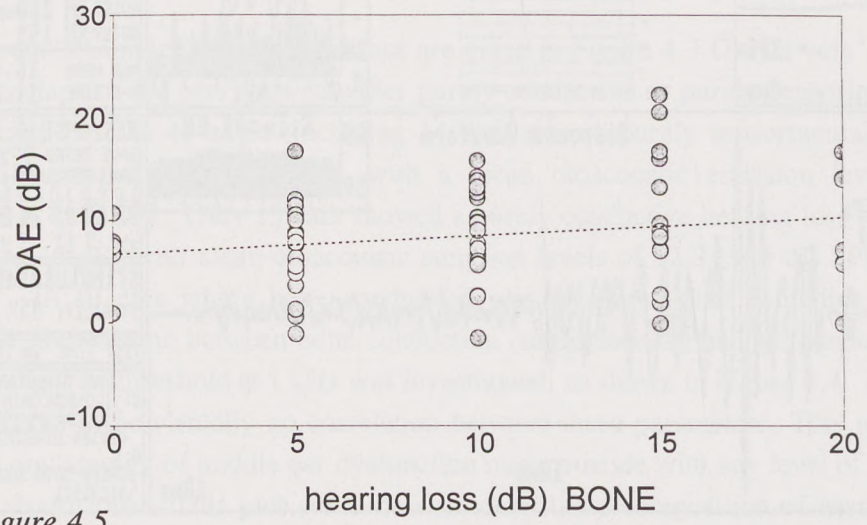


Figure 4.5
Otoacoustic emission level (ECHO in dB SPL) as a function of bone conduction hearing loss (dB) for a given total hearing loss (20 dB) at 1 kHz in 71 ears. The hearing loss ranges from purely conductive (left, 0 dB bone conduction and 20 dB air conduction loss) to purely sensorineural (right, 20 dB bone conduction and 0 dB air conduction loss). There is a small positive correlation ($p=.21$), which is not statistically significant ($p>0.05$). This means the influence of the middle ear on OAE level does not exceed that of the inner ear.

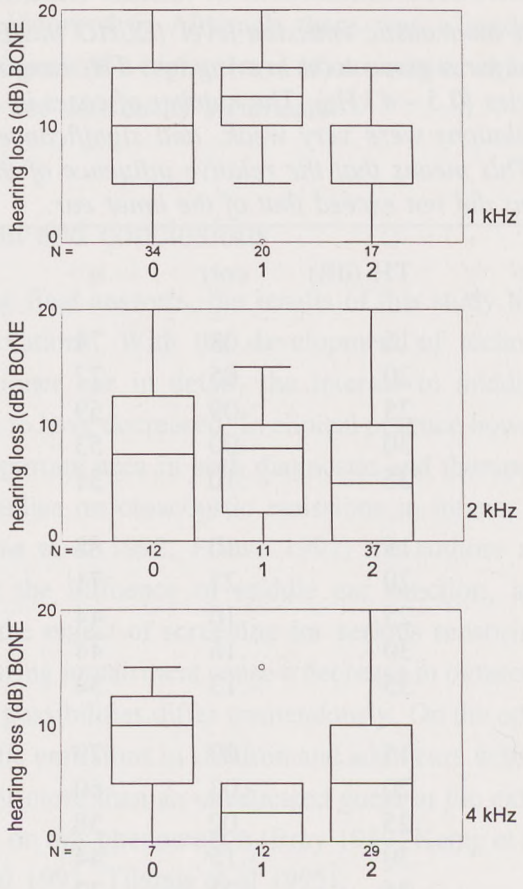


Figure 4.6
Visually scored narrowband OAE response at three frequencies (1, 2 and 4 kHz) related to bone conduction threshold, for groups of ears with 20 dB total hearing loss (n=71,60,48 respectively). The hearing loss ranges from purely conductive (bottom) to purely sensorineural (top); the OAEs from absent (0) to definite (2). There are no significant differences between the groups, though at 4 kHz ears with conductive losses tend to show higher emission levels.

drawing a line from 20 dB on the Y-axis (purely conductive hearing loss of 20 dB) to 20 dB on the X-axis (purely sensorineural hearing loss of 20 dB). The OAE level (ECHO) of these ears (with a total hearing loss of 20 dB) as a function of bone conduction threshold was displayed in Figure 4.5, as an example for the rest of the analysis. It appeared that there was a very weak positive correlation between bone conduction threshold and otoacoustic emission level, which did not reach statistical significance. In other words: the influence on otoacoustic emissions of the middle ear did not exceed that of the inner ear.

TABLE 4.1 OTOACOUSTIC EMISSIONS IN MIXED HEARING LOSSES

Correlation between otoacoustic emission level (ECHO in dB SPL) and bone conduction threshold for a given total hearing loss TH, ranging from 15 to 40 dB, at four frequencies (0.5 - 4 kHz). The number of cases in each subgroup is indicated. All correlations were very weak, and significance levels (p) were never under 0.05. This means that the relative influence of the middle ear on otoacoustic emissions did not exceed that of the inner ear.

Freq (Hz)	TH (dB)	corr	n
500	15	-.08	74
	20	.05	77
n=329	25	.09	59
	30	-.00	53
	35	.10	31
1000	15	.10	88
	20	.21	71
n=323	25	-.10	44
	30	.16	44
	35	-.13	34
2000	15	-.09	79
	20	-.03	60
n=293	25	.02	38
	30	-.15	44
	35	.21	32
4000	15	-.00	55
	20	-.12	48
n=274	25	.22	43
	30	.19	33
	35	.00	43

The results for other frequencies and dynamic ranges (total hearing losses) were summarized in Table 4.1. None of the correlations between overall OAE level (ECHO) and bone conduction threshold was statistically significant. A more frequency specific analysis was performed by correlating the visually scored OAE response in each frequency region with the bone conduction threshold for a total hearing loss of 20 dB HL at 1, 2 and 4 kHz respectively,

as displayed in Figure 4.6. Although there was a tendency for ears with conductive losses to show a higher level of otoacoustic emissions at 4 kHz, the differences were not statistically significant.

4.4 Discussion and conclusions

Far from yielding final answers, the results of this study lead to the following interesting observations. With the development of techniques to study the function of the inner ear in detail, the interest in middle ear function and mechanics seems to have decreased. In clinical practice however, the middle ear is still a very important area in both diagnostic and therapeutic aspects.

In most studies on otoacoustic emissions in infants (Chang et al 1993, Kok 1994, Owens et al 1992, Prieve 1992) the authors are in some degree concerned about the influence of middle ear function, as this is obviously interfering with the object of screening for serious sensorineural hearing loss. Both kinds of hearing impairment cause a decrease in otoacoustic emissions, but the therapeutical possibilities differ tremendously. On the other hand, the scarce data on otoacoustic emissions in children and adult ears with conductive hearing loss do not permit more than an uneducated guess at the extent of the influence of the middle ear on this phenomenon (Bray 1989, Kemp et al 1986, Lamprecht 1991, Erwig et al 1991, Tilanus et al 1995).

In practice, it is hardly ever difficult to discern obstructions in the external ear canal in young children, and to eliminate them in order to adequately measure otoacoustic emissions (Chang et al 1993). An obstruction in the middle ear leading to impaired function may be more difficult to distinguish, especially in infants. Yet, otoscopy, tympanometry (in infants) and bone conduction threshold assessment (in children and adults) will usually be sufficient to determine the localisation of the hearing loss.

In order to evaluate the quantitative effect of middle ear dysfuction on otoacoustic emissions however, data on bone conduction thresholds (the parameter most closely linked to perception thresholds) are indispensable. Unfortunately, in the only large study on otoacoustic emissions in children with middle ear dysfunction (Erwig et al 1991), these data are lacking. Although a relatively strong influence of the middle ear is suggested by the finding that otoacoustic emissions were absent in ears with thresholds above 20 dB HL, no

comparison with sensorineural losses was made to confirm this. In our study of a large number of adult ears we found that even in ears with middle ear dysfunction, otoacoustic emissions may be found, irrespective of the underlying disease. This confirms data reported by others (e.g. Lamprecht 1991) and contradicts the supposition of Probst et al (1987).

The data from this study do not support the hypothesis that the influence of the middle ear on otoacoustic emissions exceeds that of the inner ear, as suggested in the literature (e.g. Wilson 1980, Bray 1989, Kemp et al 1990, Probst et al 1987). Possible explanations for this could be: the difference in effect is there, but remains undetectable because of the heterogeneity of the groups of ears, which blurs the comparisons made, or because of the inaccuracy of the (conventional) audiometric methods to determine the amount of sensorineural and conductive hearing loss.

As described before (Chapter 4.1) it is difficult to measure the difference between air conduction threshold and bone conduction threshold (air-bone gap) with sufficient accuracy, because "diagnostic audiometry is not a precise science.." (Lutman 1987). If the air conduction threshold is assessed within 3-5 dB (depending on frequency) and the bone conduction threshold within 6 dB, the air-bone gap may be assessed with an accuracy of 7 dB at the best. This compares not very favorably to the maximum effect of about 20 dB on otoacoustic emissions, which may therefore be obscured by the inaccurate audiometric measurement. Similarly, as noted in the previous Chapter, the prediction of a hearing threshold from the OAE level is rather inaccurate, which may obscure possible differences between the (narrow) PTA classes of 5 dB we used. Also, as mentioned in Chapter 2, a bias in the data may exist because relatively few ears with small conductive losses (< 10 dB) were included.

Another possible explanation may be some 'third factor' influencing the otoacoustic emissions response, independent from air or bone conduction thresholds (like data bias, age, stimulus level, noise floor etc). Besides, there is a possibility that the effect varies depending on frequency, as mentioned by Kemp et al (1990). The overall effect on the otoacoustic emission response as expressed by the ECHO level, could then be negligible, though a differentiation between low frequency response and high frequency response might yield opposite effects. As to the first five possibilities, we have no means to reject them, due to the inadequacies inherent to our method of study. However, the

suggestion of a frequency-dependent influence of the middle ear could semiquantitatively be scored as 'maybe true', as we found a tendency for 4 kHz responses to be less influenced by middle ear dysfunction than 1 and 2 kHz responses. In accordance with the observation by Kemp et al (in one ear!), the effect at 1 and 2 kHz was different from that in higher frequencies, which is the frequency region of best performance of the middle ear in terms of impedance matching. Though these findings could indicate a stronger influence of the middle ear on otoacoustic emissions in low frequencies, the correlations found were too weak to be of clinical importance.

In conclusion: it is very well possible that there is indeed no difference in influence on otoacoustic emissions between middle and inner ear function. Although some otoacoustic emission data on children and adults with conductive hearing losses are now available, more (experimental) research is needed to solve this audiometric conundrum.

References

Békésy G von (1939): Ueber die mechanisch-akustischen Vorgänge beim Hören. Acta Otolaryngol 27:281-296 and 388-396.

Bray PJ (1989): Click evoked otoacoustic emissions and the development of a clinical otoacoustic hearing test instrument:1-201. Thesis, Univ. London

Chang KW, Vohr BR, Norton SJ, Lekas MD (1993): External and middle ear status related to evoked otoacoustic emission in neonates. Arch Otolaryngol Head Neck Surg 119:276-282

Erwig H, Blömer E, Bauer HH (1991): Zur Evaluation transitorisch evozierter otoakustischer Emissionen bei Kindern mit Tubenbelüftungsstörungen. Laryngorhinootologie 70:635-640

Helmholtz H (1863): Ueber die Wahrnehmung der Klangfarben. In: Die Lehre von den Tonempfindungen als physiologische Grundlage für die Theorie der Musik:182-223. Braunschweig

Houwelingen JC van, Stijnen T, Strik R van (1995): Inleiding tot de medische statistiek. Bunge, Utrecht

Huizing EH (1960): Bone conduction - the influence of the middle ear. Acta Otolaryngol Suppl 155

Kemp DT, Ryan S, Bray P (1990): A guide to the effective use of otoacoustic emissions. Ear Hear 11:93-105

Kok MR (1994): Otoacoustic emissions in healthy newborns and very-low-birth-weight infants. Thesis, Rotterdam

Lamprecht A (1991): Evozierte otoakustische Emissionen bei normalhörenden und schwerhörigen Erwachsenen und Kindern. Laryngorhinootologie 70:1-4

Lutman ME (1987): Diagnostic audiometry. In Kerr AG et al (eds): Scott-Brown's

Otolaryngology: Adult audiology 244-271. Butterworths, London
Owens JJ, McCoy MJ, Lonsbury Martin BL, Martin GK (1992): Influence of otitis media on evoked otoacoustic emissions in children. Semin Hear 13:53-66
Prieve BA (1992): Otoacoustic emissions in infants and children: Basic characteristics and clinical application. Semin Hear 13:37-52
Probst R, Lonsbury Martin BL, Martin GK, Coats AC (1987): Otoacoustic emissions in ears with hearing loss. Am J Otolaryngol 8:73-81
Schilder AGM (1993): Long-term effects of otitis media with effusion in children. Thesis Nijmegen
Tilanus CC, Stenis D van, Snik AFM (1995): Otoacoustic emission measurements in evaluation of the immediate effect of ventilation tube insertion in children. Ann Otol Rhinol Laryngol 104:297-300
Wilson JP (1980): Evidence for a cochlear origin for acoustic re-emissions, threshold fine-structure and tonal tinnitus. Hear Res 2:233-252
Zielhuis GA, Rach GH, Van den Broek P (1990): The occurrence of otitis media with effusion in Dutch pre-school children. Clin Otolaryngol 15:147-153

▸ 5 AGING AND OTOACOUSTIC EMISSIONS

5.1 Introduction

After investigating and analysing the impediments middle ear dysfunction may constitute to otoacoustic emissions, we will now elaborate on the most important cause of hearing loss: cochlear dysfunction.

The influence of age on the level of otoacoustic emissions may be separated into two eras: the neonatal and the post-neonatal era. As for the first, there appears to be an increase of click evoked otoacoustic emissions in the first few days of life, probably due to clearance of amniotic fluid from the middle ear (Kok 1994). In an animal model using rats, a similar increase in distortion product otoacoustic emissions was reported for the first days of life (Lenoir and Puel 1987). They attributed this to an ongoing maturation process of the cochlea after birth. In humans, no such data are presently available, but it appears that after the first cries, otoacoustic emissions keep decreasing for the rest of human lifetime. This decrease of otoacoustic emissions with age has been observed in several studies, for all kinds of responses. We will give a short review of them.

For the first year of the post-neonatal period, a gradual decrease in click evoked otoacoustic emissions was reported by Engdahl et al (1994), due to secretory otitis media as assessed by otomicroscopy. They followed up 35 healthy infants and concluded that for screening procedures, the optimal age is 3 or 4 days post partum. A similar decrease in the first two years of life for spontaneous otoacoustic emissions was reported by Burns et al (1994). They also reported large differences between neonates and adults in the distributions of frequencies and levels of spontaneous otoacoustic emissions. In a study comparing spontaneous otoacoustic emissions in healthy children and infants to those in adults, Strickland et al (1985) found no difference in the incidence of SOAEs with age, though a significant gender difference was noted. Similarly, Bargones and Burns (1988), studying a small group of ears with suppression tuning curves for spontaneous otoacoustic emissions (infants and adults), found comparable spontaneous emissions with only slightly lower reproducibility in the young ears. To account for this, they hypothesized that the fine tuning of the auditory system may develop postnatally.

A larger study was done by Bonfils et al (1988), in 151 ears from subjects aged 2 to 88 years. Using their own equipment, they found click evoked otoacoustic emissions in 100% of the ears younger than 60 years, but only in 35% of the older ears. However, the subjective click threshold in each

age group varied considerably, being on average no less than 29±4.2 dB HL in the eldest ears. Unfortunately, they provided little information on their reference group, artifact rejection technique and statistical methods. Similar results were reported by Collet et al (1990) from a study on 93 subjects ranging in age from 6 weeks to 83 years. They found a significant correlation between increasing age and decreasing otoacoustic emissions, which they attributed to an alteration in hair cell function. Again, the age groups showed large differences in hearing threshold, which might explain the entire "age effect".

More cautious observations were made by Kemp et al (1990) who suggested that the difference between neonatal and adult otoacoustic emissions may be due to differences in meatal volume or middle ear properties, but could not exclude the possibility of an increased intrinsic emission intensity in the former. Lonsbury-Martin et al (1991) compared otoacoustic emissions in carefully defined age groups of normally hearing subjects, aged 30 to 60 years. They found a decrease in spontaneous emissions in older ears, together with higher thresholds for distortion product otoacoustic emissions. They concluded that this implies the need for standards to interpret results across ages. In a very well-described study, Norton and Widen (1990) reported a decrease of click evoked otoacoustic emissions with age for normal hearing age groups from 1 month to 30 years. Although no correlations of emissions with audiometric thresholds were given, they carefully analysed their results which led them to three factors that might possibly explain the differences found: external and middle ear maturation after birth, cochlear differences (surplus of fetal outer hair cells) or "normal cochlear wear and tear".

An elaborate investigation on different types of emissions in 42 normal hearing subjects (20-80 years old) was carried out by Stover and Norton (1993). They performed split-plot analyses of covariance to evaluate the effects of age, frequency, and hearing sensitivity on several types of emission parameters. Although their data were in agreement with those from earlier studies, they prudently concluded that hearing sensitivity explained more of the variance in the data than did age. In a study comparing three age groups (<30, 30-50, >50 yrs) a significant decrease in some otoacoustic emission parameters was reported by O-Uchi et al (1994). However, it is unclear whether this could have been be due to differences in hearing thresholds. Prieve and Falter (1995) reported on spontaneous and click evoked otoacoustic emissions in 41 adults of

two age groups (young and middle-aged) with normal hearing. They found no significant differences in OAE levels between these groups, and concluded that the age factor had no relevant influence.

We may infer from these studies that quite often the assumption is made that all cochleae with a 'normal' performance will show a decrease in OHC function with time, resulting in less otoacoustic emissions. However, it is also well-known that the hearing thresholds of normal individuals tend to increase with age; a phenomenon when socially inhibiting known as presbycusis (e.g. Bunch 1929, Davis et al 1990). This affects a wide range of parameters of (retro)cochlear function (Patterson et al 1982).

Thus, the question arises whether there really is an effect of age by itself on otoacoustic emissions (causal relation), or whether this effect is caused by hearing loss, coming with age (no causal relation). Up till now, this issue seems not to have been properly addressed. Another problem in studying this issue is that it is crucial how 'normal hearing' is defined: more specifically, if the reference group for hearing thesholds covers all ages or not. We tried to overcome this difficulty by strictly defining criteria for hearing loss, and studying the combined effects of age and hearing loss on otoacoustic emissions.

5.2 Subjects and methods

As described in full detail in Chapter 2, pure tone audiograms and click evoked otoacoustic emissions were assessed in a large group of subjects with varying degrees of hearing loss of different origins, including normal hearing subjects as well. As it is known that especially high frequency thresholds deteriorate with age, the hearing levels were averaged in two ranges: lower (250, 500, 1000 Hz) and higher (2, 4, 8 kHz) frequency ranges. In multivariate procedures a partition in three ranges was used (0.25 and 0.5, 1 and 2, 4 and 8 kHz respectively), thus covering the whole standard audiometry frequency range.

In order to correct for distortion by extremely large hearing losses, deaf ears were left out of the analysis. In some parts of the analysis, a stratification according to hearing threshold was used, e.g. all ears with thresholds of 15-20 dB HL, 20-25 dB HL, etc. Correlation and regression plots were calculated for the main otoacoustic emission parameter: overall OAE level (in dB SPL). Multiple regression analysis was performed to evaluate the effect of age in combination with hearing loss on OAE levels.

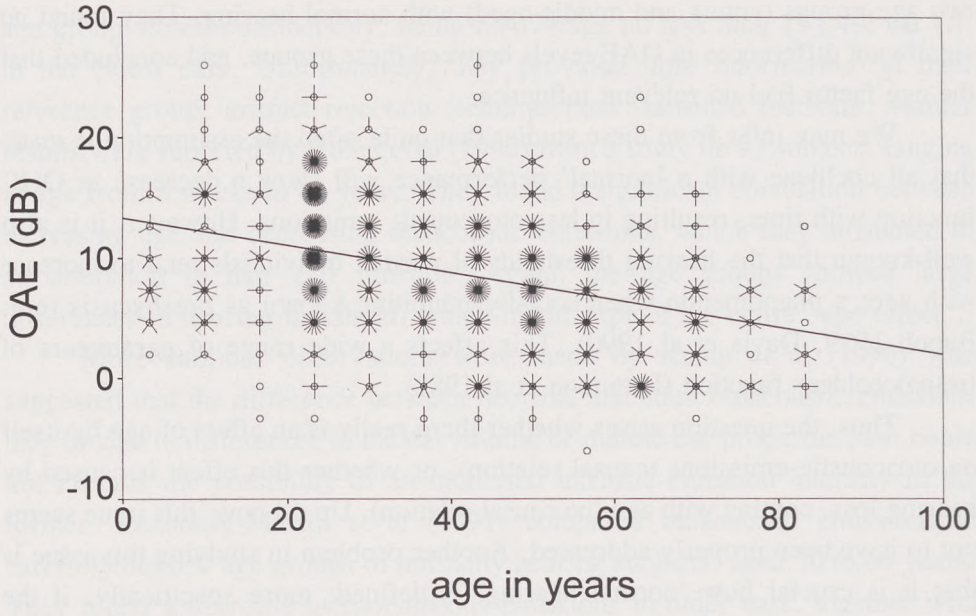


Figure 5.1
Overall otoacoustic emission level (OAE in dB SPL) as a function of age in 975 ears. The number of observations is represented by the relative density of the symbols. There is a highly significant negative correlation ($r=-.39$; $p<.00005$), indicating that old ears show less emissions than young ears. A third factor accounts for this correlation: hearing threshold.

5.3 Results

Of the 1000 ears analysed, sufficient audiometric data were available in 990 cases to be able to calculate mean hearing loss for the two frequency ranges (.25 -1 kHz, and 2-8 kHz). Leaving out totally deaf ears, 975 ears were used for evaluation of the overall relation between OAE level and age, represented in Figure 5.1. There is a negative correlation between age and overall ECHO level ($r=-.37$), with a high significance ($p<0.00005$).

Similarly, there appears to be an increase of hearing thresholds with age for both lower and higher frequencies, as illustrated in Figure 5.2. The correlation is somewhat higher for high frequencies than for low frequencies ($r=.53$ and $r=.31$, respectively), though in both cases highly significant ($p<0.00005$). The slope of the regression line is much steeper in high frequencies (.79 vs .36), indicating that high frequency thresholds deteriorate more with age than do low frequency thresholds.

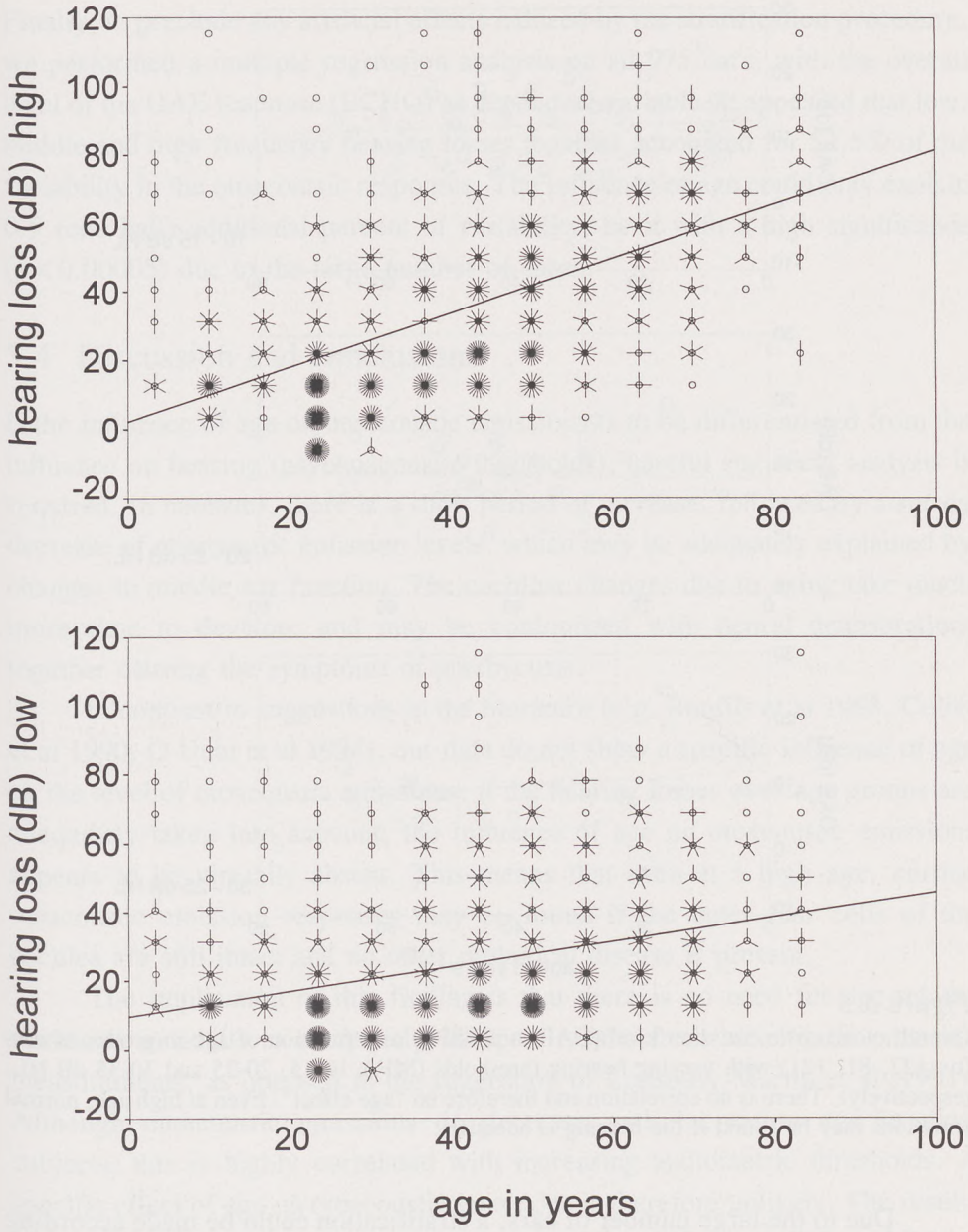


Figure 5.2
Average hearing thresholds (in dB HL) for high (2, 4, 8 kHz) and low (0.25, 0.5 and 1 kHz) frequencies as a function of age in 975 ears. The number of observations is represented by the relative density of the symbols. There is a highly significant correlation ($p < .0005$), despite the scatter of data. The high frequency thresholds increase more rapidly than do the low frequency thresholds (regression line slopes .79 and .31 respectively).

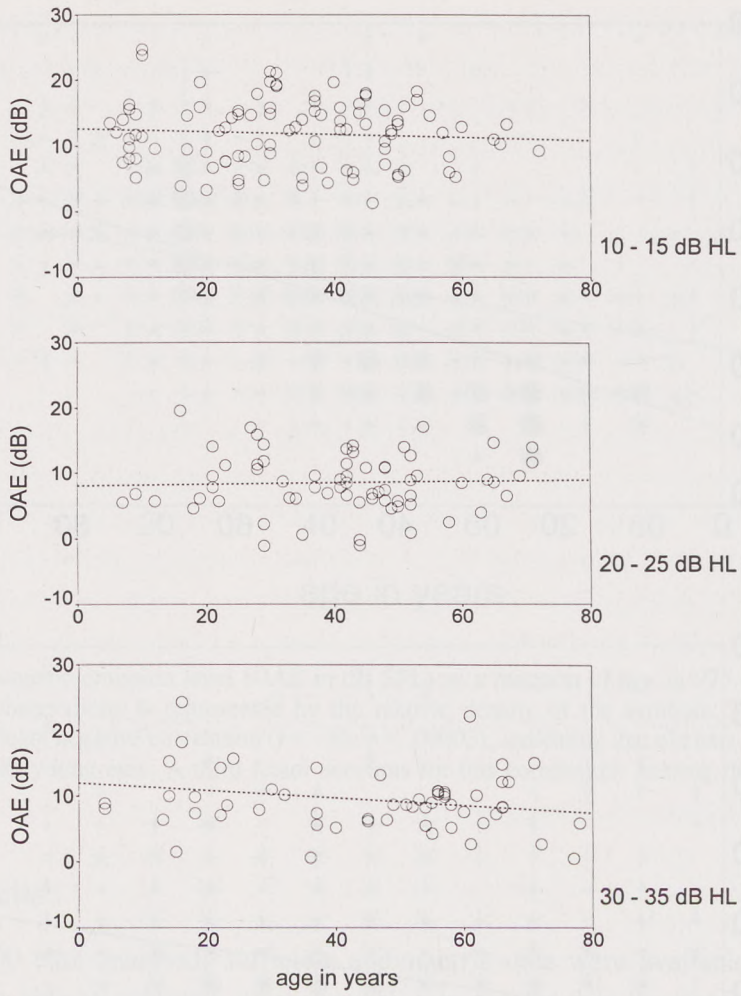


Figure 5.3
Overall otoacoustic emission level (OAE in dB SPL) as a function of age in groups of ears (n=122, 81, 121) with varying hearing thresholds (MFA 10-15, 20-25 and 30-35 dB HL, respectively). There is no correlation and therefore no "age effect". Even at high age, normal emissions may be found if the hearing is adequate.

Due to the large number of ears, a stratification could be made according to mean overall hearing threshold, yielding adequately large groups for analysis. The results are visualized in Fig 5.3, in which all ears are plotted with mean hearing thresholds of 10-15, 20-25 and 30-35 dB HL respectively. It is apparent that the otoacoustic emission level does not change with increasing age: there is no correlation between the two parameters.

Finally, to preclude any artificial effects induced by the stratification procedure, we performed a multiple regression analysis on all 975 ears, with the overall level of the OAE response (ECHO) as dependent variable. It appeared that low, middle and high frequency hearing losses together accounted for 52.5% of the variability in the otoacoustic responses. The influence of age could only explain 0.5 (one half) additional percent of variability, be it with a high significance ($p < 0.00005$) due to the large number of cases.

5.4 Discussion and conclusions

If the influence of age on otoacoustic emissions is to be differentiated from the influence on hearing (psychoacoustic thresholds), careful statistical analysis is required. In neonates, there is a short period of increase, followed by a steady decrease of otoacoustic emission levels, which may be adequately explained by changes in middle ear function. The cochlear changes due to aging take much more time to develop, and may be confounded with neural deterioration, together causing the symptoms of presbycusis.

In contrast to suggestions in the literature (e.g. Bonfils et al 1988, Collet et al 1990, O-Uchi et al 1994), our data do not show a specific influence of age on the level of otoacoustic emissions: if the hearing losses over age groups are adequately taken into account, the influence of age on otoacoustic emissions appears to be virtually absent. This means that even at a high age, normal otoacoustic emission responses may be found if the outer hair cells of the cochlea are still intact and no other otological disease is present.

The implication of this finding is that there is no need for age-related standards in adults to adequately interpret results from otoacoustic emission measurements, as opposed to the suggestion of Lonsbury-Martin et al (1991). Although otoacoustic emissions do decrease with increasing age in most subjects, this is highly correlated with increasing audiometric thresholds. A specific effect of age on otoacoustic emissions is therefore unlikely. The results of our study corroborate those reported by Stover and Norton (1993) and Prieve and Falter (1995), who studied different types of emissions in smaller groups.

There is one confounding factor in this study, which is the heterogeneity of the ears with hearing loss. In other words, the 'old ears' belong to other subjects than the 'young ears'. However, our multivariate analysis did not show significant influences on the level of otoacoustic emissions, apart from those of

the parameters mentioned above. Nonetheless, in an ideal setting to definitely prove the absence of an age effect on otoacoustic emissions, a follow-up study should be performed in a cohort covering several decades: the results of such a study will, at the earliest, be discussed by the next generation.

In conclusion: there is no specific influence of age on click evoked otoacoustic emissions. The "age effect" relates to hearing thresholds only.

References

Bargones JY, Burns EM (1988): Suppression tuning curves for spontaneous otoacoustic emissions in infants and adults. J Acoust Soc Am 83:1809-1816

Bonfils P, Bertrand Y, Uziel A (1988): Evoked otoacoustic emissions: normative data and presbycusis. Audiology 27:27-35

Bunch C (1929): Age variations in hearing acuity. Arch Otolaryngol 9:625-636

Burns EM, Campbell SL, Arehart KH (1994): Longitudinal measurements of spontaneous otoacoustic emissions in infants. J Acoust Soc Am 95(1):385-394

Collet L, Moulin A, Gartner M, Morgon A (1990): Age-related changes in evoked otoacoustic emissions. Ann Otol Rhinol Laryngol 99:993-997

Davis AC, Ostri B, Parving A (1990): Longitudinal study of hearing. Acta Otolaryngol Suppl Stockh 476:12-22

Engdahl B, Arnesen AR, Mair IW (1994): Otoacoustic emissions in the first year of life. Scand Audiol 23(3):195-200

Kemp DT, Ryan S, Bray P (1990): A guide to the effective use of otoacoustic emissions. Ear Hear 11:93-105

Kok MR (1994): Otoacoustic emissions in healthy newborns and very-low-birth-weight infants. Thesis Rotterdam.

Lenoir M, Puel JL (1987): Development of 2f1-f2 otoacoustic emissions in the rat. Hear Res 29:265-271

Lonsbury-Martin BL, Cutler WM, Martin GK (1991): Evidence for the influence of aging on distortion-product otoacoustic emissions in humans. J Acoust Soc Am 89:1749-1759

Norton SJ, Widen JE (1990): Evoked otoacoustic emissions in normal-hearing infants and children: emerging data and issues. Ear Hear 11:121-127

O-Uchi T, Kanzaki J, Satoh Y, Yoshihara S, Ogata A, Inoue Y, Mashino H (1994): Age-related changes in evoked otoacoustic emission in normal-hearing ears. Acta Otolaryngol Suppl Stockh 514:89-94

Patterson RD, Nimmo-Smith I, Weber DL, Milroy R (1982): The deterioration of hearing with age: Frequency selectivity, the critical ratio, the audiogram, and speech threshold. J Acoust Soc Am 72(6):1788-1803

Prieve BA, Falter SR (1995): COAEs and SSOAEs in adults with increased age. Ear Hear 16:521-528

Stover L, Norton SJ (1993): The effects of aging on otoacoustic emissions. J Acoust Soc Am 94(5):2670-81

Strickland EA, Burns EM, Tubis A (1985): Incidence of spontaneous otoacoustic emissions in children and infants. J Acoust Soc Am 78:931-935

▸ 6 DIFFERENTIAL DIAGNOSIS BY OTOACOUSTIC EMISSIONS

6.1 Introduction

In most cases the determination of the cause of the hearing loss in a patient is not very difficult. A careful history, otomicroscopic examination, pure tone audiometry and tympanometry will lead to an almost certain diagnosis in the majority of patients. However, there are some groups of related disorders which may be difficult to discern. In the literature on otoacoustic emissions, most reports on differential diagnosis concern the distinction between cochlear and retrocochlear pathology, as these both induce a sensorineural hearing loss, and the therapeutic consequences of this distinction are evident.

For example, Bonfils et al (1988) reported on click evoked otoacoustic emissions in 28 acoustic neuroma patients: 32% showed emissions similar to those found in ears with losses due to other etiologies. This led them to the hypothesis that acoustic tumors usually produce a cochlear hearing loss. Robinette (1992) evaluated 61 acoustic neuroma patients, and found click evoked OAEs in 20% of ears with mild to moderate hearing losses. Patuzzi (1993) gave an account of the use of otoacoustic emissions for the categorization of cochlear and retrocochlear lesions. However, with modern imaging techniques (CT and MRI scans), this problem is practically solved, even without auditory brain stem response audiometry (ABR).

Some puzzles remain, though. For example, in children it may be difficult to attribute an observed hearing loss to either middle ear effusion (very common), testing inadequacies (lack of attention) or sensorineural deficits (very rare). In adults, when pure tone audiometry is possible, the involved frequencies of the hearing loss may give a clue. The low frequency loss typical of Menière's disease may be distinguished from middle ear disease (e.g. fluid, stapes fixation) by measuring bone conduction thresholds. With high frequency hearing losses however, in some cases it may be difficult to distinguish between presbycusis and noise induced hearing loss. One may even encounter difficulties in discriminating between 'normal' and 'abnormal' hearing as in psychogenic hearing loss, aggravation or malingering.

Nonetheless, these last two dilemmas (age or noise effect, genuine or pretended loss) may have important occupational and medicolegal consequences. Besides, in order to disclose psychogenic hearing loss, more cumbersome methods (Stenger test, ABR) may be needed (Rodenburg 1989, Martin 1994).

We will therefore examine the possibilities otoacoustic emissions offer in these circumstances. In their practical survey on otoacoustic emissions, Kemp et al (1986) mentioned no influence of the kind of pathology on the expected level of the response. However, only a few diagnostic categories were studied, the emphasis being on the level rather than the cause of the hearing loss.

It has been reported that in ears with noise induced high frequency hearing loss, there is a significant decrease of spontaneous and click evoked otoacoustic emissions, as compared to ears with similar loss of probable hereditary etiology (Probst et al 1987). This could be interpreted as a high sensitivity of otoacoustic emissions for sensory cell damage to cochlear frequency regions that appear to be audiometrically normal. However, to our knowledge this interesting finding has not been confirmed by other studies, although click evoked otoacoustic emissions seem to be very sensitive to noise effects (Plinkert et al 1995). Another example of the supposedly high sensitivity of otoacoustic emissions to cochlear function was reported by Martin et al (1990). They used DP otoacoustic emissions to detect a small notch in the audiogram of a young adult with noise exposure.

In a differential diagnostic case study of a boy with unilateral profound hearing loss by Lutman et al (1989), good cochlear function was demonstrated by click evoked otoacoustic emissions, indicating a retrocochlear disorder. Brain stem audiometry and electrocochleography ruled out the possibility of a psychogenic hearing loss. Some examples of persistent click evoked otoacoustic emissions in cases of psychogenic hearing loss (pseudohypacusis) were given by Robinette (1992), together with conventionally obtained audiometric data. He concluded that click evoked otoacoustic emissions may be useful in uncovering this condition.

In summary, although some data on differential diagnosis by otoacoustic emissions in the two fields mentioned above are available, a systematic study of the possibilities to distinguish between noise and age effects or malingering and normal hearing by measuring otoacoustic emissions is still lacking. Specifically, we sought to answer the following two questions: is it possible in cases of high frequency sensorineural hearing loss to distinguish between noise effects and presbycusis by measuring otoacoustic emissions? What role can measurement of click evoked otoacoustic emissions play in cases of suspected psychogenic hearing loss?

6.2 Subjects and methods

In our population of 500 patients and controls, all ears with adequate otoacoustic emission (n=990) and audiometric (n=972) data were evaluated. The cause of the hearing loss was attributed for each ear to one of twelve diagnostic categories, as described in Chapter 2.3.1.

Apart from a careful medical history and otomicroscopic inspection, pure tone audiometry and click evoked otoacoustic emission measurements were performed. Tympanometry, stapedial reflex measurements, ABR audiometry, CT or MRI scans, and blood tests were performed when necessary to obtain an adequate degree of certainty concerning the diagnosis. A rather large group of patients with psychogenic hearing loss and a substantial number of patients with noise induced hearing loss were recruited from the Utrecht Central Military Hospital.

First, the overall variation of otoacoustic emissions level (OAE) and hearing loss according to diagnosis was screened. Secondly, the ears from the two differential diagnostic problem groups mentioned above were analysed with respect to their hearing thresholds and otoacoustic emissions as expressed by the parameters overall otoacoustic emission level (ECHO) and reproducibility of the response (REPRO). The ears of all patients with presbycusis were compared to those with noise induced hearing loss. A similar comparison was made between the ears of malingerers, normals and matched controls. The control group was composed of all ears with a real, moderate hearing loss (MFA between 15 and 40 dB HL), with an age limit of 40 years to get comparable groups. Likewise, in this comparison pretended losses of 15 to 40 dB were considered. Statistical procedures were performed as described earlier (Chapter 2.3.4).

6.3 Results

The otoacoustic emission levels in 990 ears are displayed in Figure 6.1 as a function of diagnosis. There is a considerable variation in overall otoacoustic emission level (ECHO), which we also see in the respective mid frequency average hearing thresholds, represented in Figure 6.2. At first sight, no specific pattern is distinguishable which could not be explained by the already noticed negative correlations between hearing thresholds and otoacoustic emissions (see Chapters 3, 4 and 5).

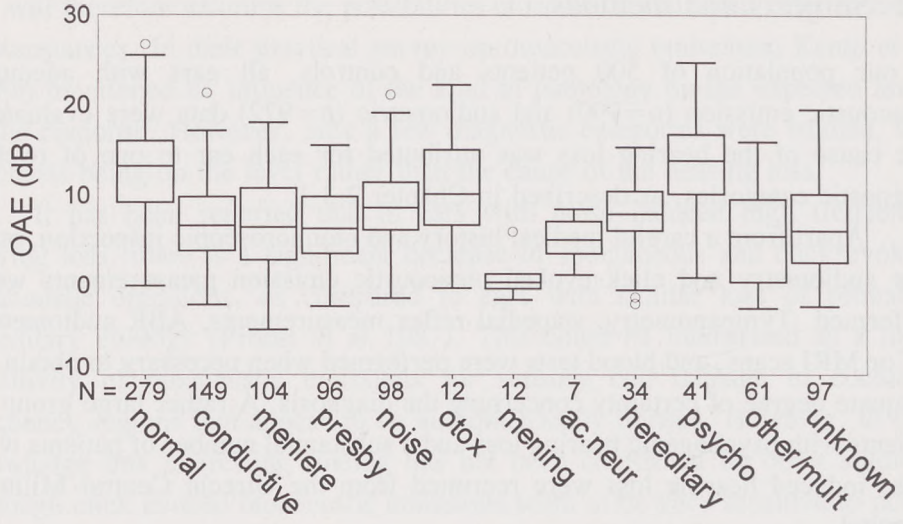


Figure 6.1

Overall otoacoustic emission levels (OAE in dB SPL) and diagnosis in 990 ears, showing large differences in pattern. The bars indicate median values; 50% of cases have values within the box. The number of ears in each diagnostic group is noted below each box. The diagnostic groups are: normal hearing, conductive loss, Menière's disease, presbycusis, noise induced hearing loss, ototoxicity, meningitis, acoustic neuroma, hereditary loss, psychogenic loss, other/multiple causes, unknown etiology.

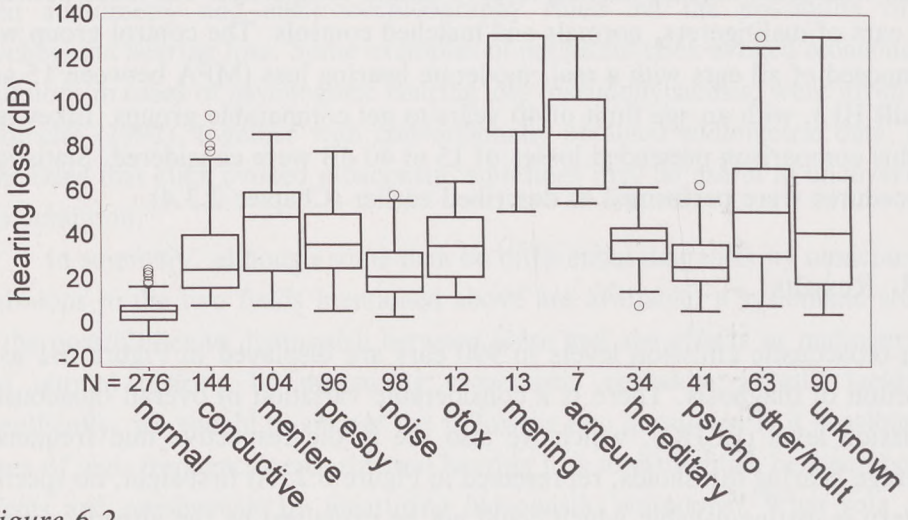


Figure 6.2

Mid frequency average hearing thresholds (MFA in dB HL) and diagnosis in 972 ears. There is an inverse relation with the otoacoustic emissions levels of Figure 6.1 (same diagnostic groups). The number of ears in each diagnostic group is noted below each box.

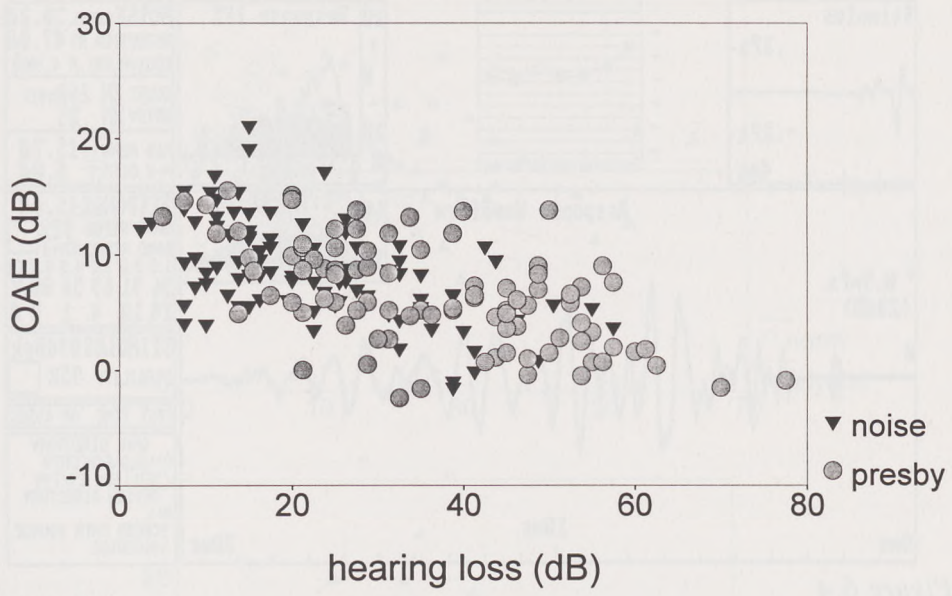


Figure 6.3
Otoacoustic emission levels (OAE in dB SPL) and hearing thresholds (MFA in dB HL) in ears with noise induced hearing loss (n=98) or presbycusis (n=96). The groups show too much overlap to be distinguished from eachother by means of otoacoustic emissions.

In case of specific differential diagnostic problems, much depends on the groups being compared. In 96 ears of presbycusis patients, mean hearing thresholds (MFA) were 36.1±15.6 dB HL and otoacoustic emission level (ECHO) was 6.6±4.5 dB SPL. The comparable group of 98 ears of patients with noise induced hearing loss showed values of 22.5±12.0 dB HL (MFA) and 8.8±4.2 dB SPL respectively. It was not possible to distinguish between these groups by comparing otoacoustic emission levels, as visualized in Figure 6.3. Analysis of variance with the hearing loss as covariate confirmed this impression (p=.655).

The hearing thresholds in patients with psychogenic hearing loss are difficult to assess accurately by psychoacoustic tests like the pure tone audiogram. The results of the otoacoustic emissions measurements were very convincing, though. An example of a high otoacoustic emission level in a patient with apparently very poor hearing as measured by pure tone audiometry is given in Figure 6.4. In Table 6.1 a summary is given, comparing pure tone thresholds and otoacoustic emission parameters in psychogenic hearing 'loss', normals and controls. The mean ages of these three groups did not show

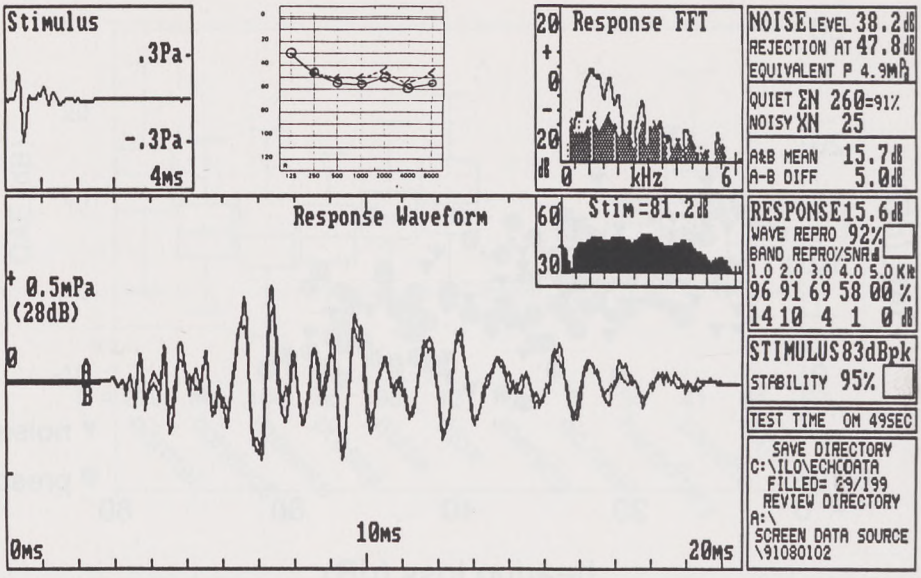


Figure 6.4
Example of high level otoacoustic emissions in a patient with a substantial hearing loss as measured by pure tone audiometry. Such discrepancy may indicate a psychogenic origin.

Table 6.1 OAEs AND HEARING IN THREE DIAGNOSTIC GROUPS

Hearing thresholds (MFA) and otoacoustic emission parameters (OAE, REPRO) for three groups of ears: psychogenic hearing loss (33), normals (272) and matched controls (109). Although the hearing 'loss' in the psychogenic group was similar to that of the controls, the otoacoustic emissions levels and reproducibility equaled those observed in the normal ears.

Diagnosis	MFA	OAE	REPRO
psycho	26.7±6.2	13.7±5.9	85 (22-98)
normals	4.8±5.5	12.7±4.9	90 (-4-99)
controls	25.5±8.7	8.2±4.2	49 (-21-98)

MFA = mean hearing threshold 0.5-4 kHz in dB HL
OAE = mean overall otoacoustic emission level in dB SPL
REPRO = median reproducibility of response in % (min-max)

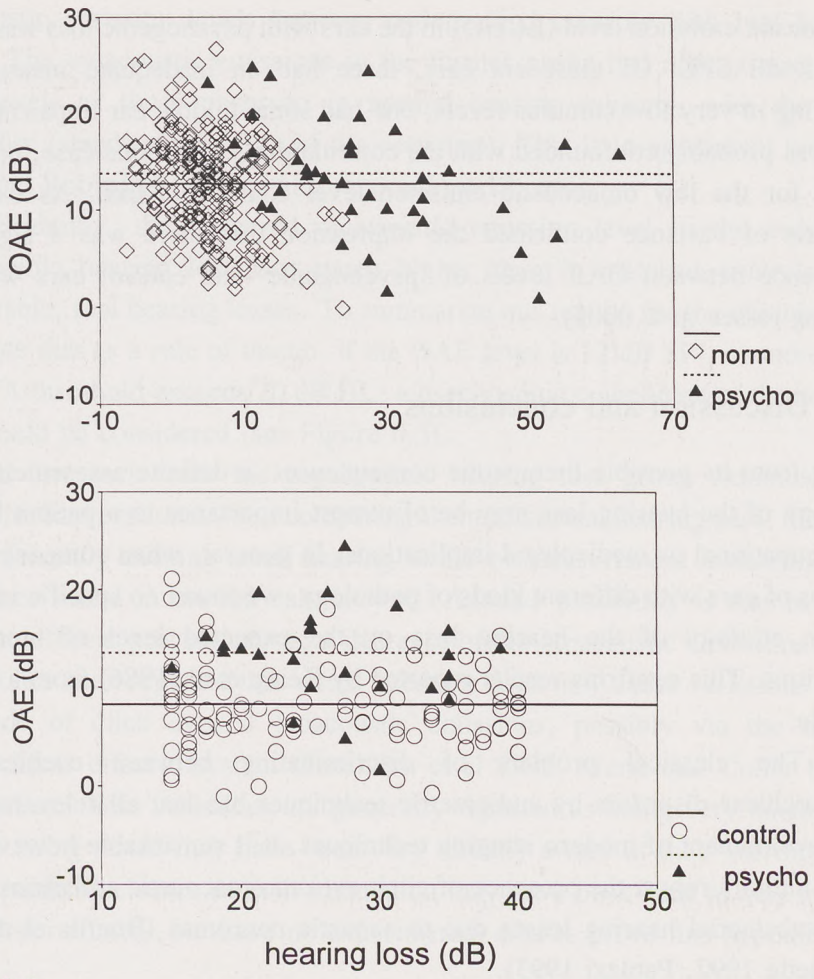


Figure 6.5
Otoacoustic emission levels (OAE in dB SPL) in psychogenic hearing loss compared to normal hearing subjects and to matched controls, as a function of mean hearing threshold (MFA in dB HL). The lines indicate group means. Although the pure tone audiometric hearing losses in the psychogenic group are similar, the observed emission levels are higher than in the control group, and comparable to those found in normal ears.

significant differences. Although the average hearing thresholds in the matched control group are the same as those in the psychogenic group, the latter shows a significantly higher level of emissions, which indeed is comparable to that usually found in normal ears. A graphic representation of the respective otoacoustic emission levels and hearing thresholds for 'psychogenic', normal and control ears is given in Figure 6.5. In all but six cases, the overall

otoacoustic emission level (ECHO) in the ears with psychogenic loss was higher than 8 dB SPL. Of these six ears, three had an inadequate measurement resulting in very low stimulus levels, one had some middle ear impairment and one was probably confounded with the contralateral ear. In one case, no definit cause for the low otoacoustic emission level could be found. As expected, analysis of variance confirmed the impression that there was a significant difference between OAE levels of 'psychogenic' and control ears with real hearing losses ($p < .0005$).

6.4 Discussion and conclusions

Apart from its possible therapeutic consequences, a definite assessment of the etiology of the hearing loss may be of utmost importance to a patient because of occupational or medicolegal implications. In general, when comparing large groups of ears with different kinds of pathology, we found no specific influence of the etiology of the hearing loss on the expected level of otoacoustic emissions. This confirms results reported by Kemp et al (1986) from a smaller sample.

The classical problem of discriminating between cochlear and retrocochlear disorders by audiometric techniques has lost all relevance since the development of modern imaging techniques. It is remarkable however, that some authors report the presence of click evoked otoacoustic emissions in ears with substantial hearing losses due to acoustic neuromas (Bonfils et al 1988, Robinette 1992, Patuzzi 1993).

In comparing a group of presbycusic patients to patients with noise-induced hearing loss, otoacoustic emissions proved to be of no help in distinguishing the cause of the ailment. Therefore, we could not confirm the high sensitivity of otoacoustic emissions to noise effects when compared to hereditary causes of hearing loss, as observed by Probst et al (1987). However, our data comprise a larger sample (194 ears versus 21 ears) and there is more similarity between the two diagnostic groups in our series. Both these aspects may account for a different outcome. Also, the basis for categorization of patients is a (subjective) careful medical history, which relies heavily on the memory and cooperation of the patient as well as on the skills and interpretation of the researcher.

In cases of psychogenic hearing loss, there was a distinct difference in

otoacoustic emission levels between patients and controls with real hearing losses. The otoacoustic emissions in the former group had approximately the same levels as those observed in normal hearing subjects, with the same variability (standard deviation of the response). This is in agreement with the data from Robinette (1992), who reported on 12 cases.

Evidently, the observed otoacoustic emission level in the ears with psychogenic hearing loss was much higher than in matched controls with comparable, real hearing losses. To summarize our results for the clinician, we may state that as a rule of thumb, if the OAE level is 12 dB SPL or more, and the MFA threshold exceeds 20 dB HL, a psychogenic component of the hearing loss should be considered (see Figure 6.5).

A few ears from the psychogenic hearing loss group exhibited less emissions than expected when comparing them to normal hearing ears: this may be due to really existing small hearing losses or measurement instabilities, as sometimes found in normal ears as well. Another possibility is that in some cases an efferent process caused a decrease of the otoacoustic emissions level.

It has been reported that visual attention tasks may cause variations in the amplitude of click evoked otoacoustic emissions, possibly via the medial olivocochlear efferent system (Froehlich et al 1993, Meric and Collet 1994). Nonetheless, these variations are generally reported as being very small. The subjects being tested may have been very visually aware of their surrounding, as a possible disclosure of their simulation may have been hard to stay at ease with. Unfortunately, we have no experimental data to prove this hypothesis at present.

In conclusion: click evoked otoacoustic emissions levels did not differ significantly in two large groups of ears with high frequency hearing loss of different etiology (presbycusis and noise trauma). Nonetheless, measurement of otoacoustic emissions can be a valuable and effective tool in uncovering psychogenic hearing loss, which has implications for examination procedures.

References

Bonfils P, Uziel A, Pujol R (1988): Evoked otoacoustic emissions: a fundamental and clinical survey. ORL J Otorhinolaryngol Relat Spec 50:212-218

Froehlich P, Collet L, Morgon A (1993): Transiently evoked emission amplitudes change with changes of directed attention. Physiol Behav 53(4):679-82

Kemp DT, Bray P, Alexander L, Brown AM (1986): Acoustic emission cochleography - practical aspects. Scand Audiol Suppl 25:71-95

Lutman ME, Mason SM, Sheppard S, Gibbin KP (1989): Differential diagnostic potential of otoacoustic emissions: a case study. Audiology 28:205-210

Martin FN (1994): Pseudohypacusis. In Katz J (ed) Handbook of clinical audiology:553-67

Martin GK, Ohlms LA, Franklin DJ, Harris FP, Lonsbury Martin BL (1990): Distortion product emissions in humans. III. Influence of sensorineural hearing loss. Ann Otol Rhinol Laryngol Suppl 147:30-42

Meric C, Collet L (1994): Differential effects of visual attention on spontaneous and evoked otoacoustic emissions. Int J Psychophysiol 17(3):281-289

Patuzzi R (1993): Otoacoustic emissions and the categorization of cochlear and retrocochlear lesions. Br J Audiol 27(2):91-5

Plinkert PK, Hemmert W, Zenner HP (1995): Comparison of methods for early detection of noise vulnerability of the inner ear. HNO 43(2):89-97

Probst R, Lonsbury Martin BL, Martin GK, Coats AC (1987): Otoacoustic emissions in ears with hearing loss. Am J Otolaryngol 8:73-81

Robinette MS (1992): Clinical observations with transient evoked otoacoustic emissions with adults. Semin Hear 13:23-35

Rodenburg (1989): Audiometrie: methoden en klinische toepassingen. Coutinho, Muiderberg

▸ 7 OTOACOUSTIC EMISSIONS IN MENIÈRE'S DISEASE - FREQUENCY SPECIFICITY AND TIME EFFECTS

7.1 Introduction

One of the more common causes of sensorineural hearing loss is the enigmatic disease originally described by Prosper Menière (Menière 1861). The classical triad of vertigo attacks, hearing loss and tinnitus may be more or less complete, which renders the certainty of the diagnosis a difficult matter in some patients. The symptoms may appear in one or both ears, and show a varying intensity, though usually the hearing tends to deteriorate in the long run while the vertigo attacks diminish. The origin of the disorder is not yet known. Endolymphatic hydrops is thought to be a secondary phenomenon that plays a role in the development of the symptoms (Hallpike and Cairns 1938).

In the literature, only a few reports on the use of otoacoustic emissions in patients with Menière's disease may be found. Bonfils et al (1988) described an increased incidence of click evoked otoacoustic emissions in 9 out of 30 ears with Menière's disease after glycerol administration. Unfortunately, neither inclusion criteria nor audiometric data were given. A somewhat puzzling report was given by Bartoli et al (1992), who found click evoked otoacoustic emissions in 38% of 20 Menière ears with average hearing thresholds of more than 45 dB HL in the midfrequencies (0.5 to 2 kHz).

A thorough study was performed by Harris and Probst (1991) who measured click and tone-burst evoked emissions in 31 Menière patients, yielding comparable results for the two kinds of stimuli. They found a strong influence of hearing thresholds on the presence of click evoked otoacoustic emissions. Interestingly, the contralateral normal ears in their patients showed less emissions both in amplitude and spectral peaks when compared to control ears from a normative database, though the hearing thresholds in these ears were essentially normal. Recently, Van Huffelen et al (1995) reported on click evoked and distortion product otoacoustic emissions in 40 Menière patients. Like Bartoli et al (1992), they found emissions in ears with hearing thresholds of up to 35-60 dB HL, but the emission levels in contralateral ears did not differ significantly from normal controls. Possible applications for patient categorization or monitoring of therapeutic effects were suggested.

A more or less diagnostic clue when suspecting Menière's disease is the low-frequency, sensorineural hearing loss found in this disorder, which is in contrast with the more high-frequency losses typical of presbycusis or noise

trauma. The presence of otoacoustic emissions (both TE and DP) at different frequencies was studied by Gorga et al (1993) to distinguish normal from abnormal ears. They found that at high frequencies, otoacoustic emissions performed better than at low frequencies, mainly because of background noise.

The question of the frequency specificity of otoacoustic emissions is a very complicated one (e.g. Wit et al 1981, Lind and Randa 1989, Kemp et al 1990). According to several authors a certain frequency specificity (especially of distortion product emissions) may be supposed (e.g. Horner and Cazals 1989, Lonsbury-Martin et al 1990, Avan and Bonfils 1993). In a study on patients with either acoustic trauma or presbycusis, Avan et al (1993) found a significant correlation between the n kHz otoacoustic emission threshold and the 2n kHz hearing threshold. They suggested that otoacoustic emission thresholds and amplitudes may be proportional to the total number of residual active sites along the organ of Corti. Nonetheless, it is important to realize that there may be a significant interaction between the cause of the disease and the level and nature of the observed hearing loss, which hampers study of these factors separately (see also Chapter 6). Therefore, only practical aspects of frequency specificity were investigated in this study.

One of the most striking features of Menière's disease is its fluctuating sensorineural hearing loss in the early phase of the disease. As it is often desirable to have repeated audiometric measurements of the affected ears, an investigation of the use of otoacoustic emissions in following up these patients seems promising. Evidently, such a quick test could be especially useful when performed repeatedly, characterizing cochlear mechanical status in long term monitoring (Kemp et al 1990). In a variety of clinical entities other than Menière's disease, this dynamic nature of SNHL may be important to discern, which requires substantial efforts from the involved audiologists (Hall et al 1993). As a model for long-term fluctuations the glycerol test may be used; this test causing short-term improvement of hearing in the early phase of Menière's disease (Klockhoff and Lindblom 1966). For this reason, a positive glycerol test has since long been used as a diagnostic criterium.

In summary: although some interesting data on otoacoustic emissions in Menière patients are available, a comprehensive investigation of what happens to OAEs in these patients when hearing levels vary with frequency or with time is still lacking. Therefore, we intended to answer these questions: is it possible

to obtain frequency specific information on cochlear function by click evoked otoacoustic emissions? Do click evoked otoacoustic emissions follow audiometric changes observed after glycerol ingestion?

7.2 Subjects and methods

In 30 patients with Menière's disease, glycerol tests were performed. Criteria for inclusion were in accordance with the Utrecht definition of Menière's disease (Van Deelen 1986, Schmidt and Huizing 1992): a unilateral or bilateral sensorineural hearing loss, (a history of) vertigo attacks and (a history of) tinnitus, without any evidence of a possible other cause for the symptoms apart from Menière's disease, as proven by CT-scan, ABR audiometry and blood tests. In total, 48 ears were studied both audiometrically and otoacoustically; in 12 patients only one side was measured, in 18 both sides.

Hearing levels (0.5 to 4 kHz) and otoacoustic emissions were measured before glycerol ingestion (2.6 ml/kg body weight) and after 1, 2, 3 and 4 hours. Hearing thresholds were assessed by Békésy audiometry, from which plots were drawn to determine the fluctuation of hearing in the studied midfrequency region. The effects of glycerol ingestion were scored as follows: a) definite effect: improvement (or deterioration) of hearing of at least 10 dB difference in two or more frequencies in one or more post glycerol measurements; b) dubious or slight effect: a shift in threshold of less than 10 dB or in only one frequency, or c) no effect at all: changes not complying with the above criteria.

Of the otoacoustic emissions, the three main parameters were taken into account: ECHO level, reproducibility and spectral content of the response. The otoacoustic data were visually scored in three frequency regions (0.5-1, 1-2, 2-4 kHz) as showing definite, possible or no emissions. Criteria for definite emissions were: emission level at least 10 dB above noise floor, and bandwidth of the peak of at least 150 Hz. Possible (dubious) emissions were all responses above the noise floor, though not complying with the above-mentioned criteria, whereas no emissions were scored when there was no response above the noise floor in a certain frequency region (see also Chapter 2.3.3). Artifacts were excluded by visually screening stimulus and response time windows.

As the normal variability in response level over several hours was found to be approximately 10% in ECHO level (dB SPL) in a control group of ears (Ch 3.3), an increase (or decrease) of at least 30% in otoacoustic emissions

level (ECHO in dB SPL) was considered a definite effect (+) of glycerol. A slight variation was scored dubious (±), and no difference (< 10%) was scored negative (-). Statistical analysis including multiple analysis of variance, was performed by means of the SPSS/PC+ package.

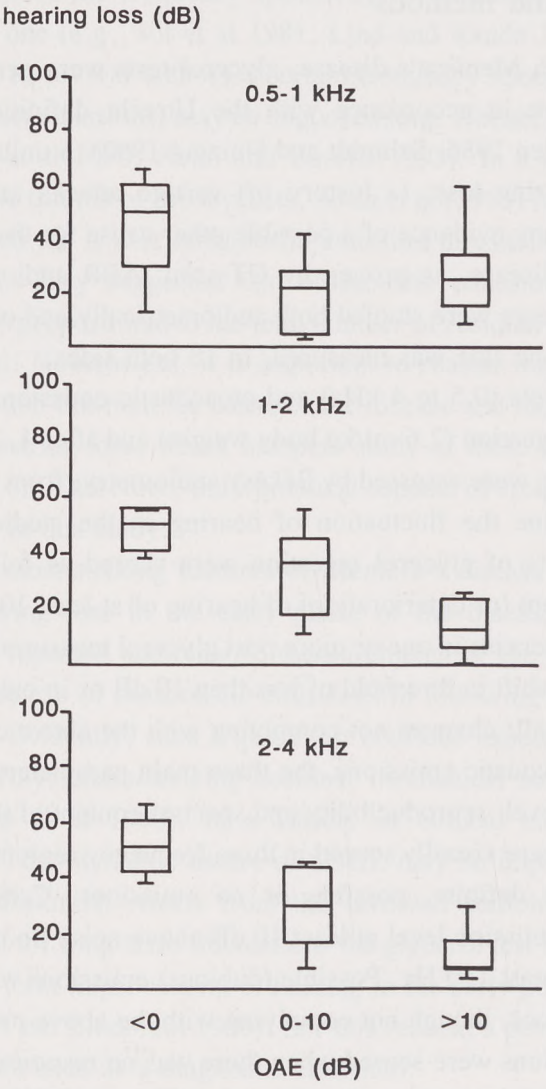


Figure 7.1
Hearing loss (dB) and narrowband otoacoustic emissions above noise floor in three frequency regions (48 ears). The OAEs are visually scored as being absent (< 0 dB), dubious (0-10 dB) or distinct (> 10 dB). In every frequency region, the ears with definite emissions have lower thresholds than the ears without emissions, as confirmed by multivariate analysis.

7.3 Results

7.3.1 Frequency specificity of OAE level and hearing threshold

The narrowband otoacoustic emission level in relation to hearing threshold in three frequency regions is represented in Figure 7.1. In all frequency regions, the ears showing definite emissions had significantly smaller median hearing losses than those that did not show emissions. The ears with dubious emissions had a median threshold between that of the former groups, except for the lowest frequency band (0.5 - 1 kHz).

The data were logarithmically transformed to compensate for the non-normality of their distribution, to perform analysis of variance. The influence of hearing loss in a certain frequency region on the level of the otoacoustic emissions in that same frequency region was highly significant ($p < .00005$). However, some interaction between the different spectra was noted: this means the losses in different frequency regions were not independent from each other.

7.3.2 Time effects of glycerol on OAEs and hearing threshold

In 48 ears (37 affected and 11 non-affected), the changes in hearing level and OAE level were compared before and after glycerol ingestion. The results are represented in Table 7.1, and the totals are summarized in Table 7.2. Correlation and regression plots of the groups of ears did not show a clear picture of the variations in time in individual cases. Hearing levels changed in 21 ears, otoacoustic emissions in 16. No change in hearing threshold was observed in 10 ears, and a dubious change in 17. For otoacoustic emissions, these figures were 13 and 19, respectively. In 30 ears, the effect on hearing and otoacoustic emissions was the same, in 4 opposite, and in 14 ears somewhere in between. The correlation between audiometric and otoacoustic effect is fair to good, Cohen's kappa being 0.43 (Fleiss 1981). In the remaining 12 ears, no conclusions could be drawn due to missing values.

A distinct example of a positive glycerol effect is given in Figure 7.2. This patient showed a considerable improvement in hearing (almost 20 dB) 1.5 hours after glycerol ingestion, which was closely followed by an increase in otoacoustic emission level. Another patient exhibited a combination of steady OAE levels and a gradual, step by step increase in audiometric threshold after glycerol ingestion. Two patients showed an initial improvement of pure tone

Table 7.1 GLYCEROL INDUCED CHANGES IN OAE AND HEARING

Effect of glycerol on midfrequency hearing levels (aud) and otoacoustic emissions (OAE) in right and left ears of 30 Menière patients. Affected ears (n=37) are indicated by + in the "aff" column. In the majority of cases (30/48), both parameters show the same effect. The glycerol effect is most often an amelioration of hearing impairment, but may also be a (temporary) deterioration. The exact criteria for scoring of the changes are mentioned in the text. A summary of the results is found in the next Table 7.2

	RIGHT			LEFT		
n	aff	aud	OAE	aff	aud	OAE
1	+	+	+	+	+	+
2	+	±	--	--	.	.
3	.	.	.	--	--	--
4	+	+	+	--	.	.
5	+	+	+	--	+	--
6	+	+	+	+	+	+
7	+	+	±	+	+	--
8	+	±	+	--	--	--
9	+	±	+	--	.	±
10	+	--	--	--	--	--
11	+	±	±	+	±	±
12	+	+	±	--	.	+
13	--	.	±	+	--	--
14	+	±	±	--	.	±
15	.	.	.	+	±	--
16	.	.	.	+	+	+
17	+	+	+	--	±	±
18	--	--	±	+	±	±
19	--	.	--	+	+	±
20	--	.	+	+	+	+
21	+	+	±	--	--	±
22	--	±	±	+	+	±
23	+	±	--	+	+	±
24	--	+	+	+	±	±
25	+	±	±	+	+	+
26	+	.	±	.	+	--
27	+	±	±	+	--	+
28	+	±	+	+	+	+
29	+	--	--	--	±	±
30	+	±	±	--	--	--

+ evident effect ± dubious effect -- no effect . missing value

Table 7.2 CORRELATION BETWEEN CHANGES IN OAE AND HEARING

Correlation between audiometric (HT) and otoacoustic (OAE) effect of glycerol ingestion in 48 ears of Menière's patients. Cohen's kappa is 0.43, indicating a fair to good agreement beyond chance between these two measurements.

		OAE level			
		+	±	--	
HT	+	12	6	3	21
	±	3	11	3	17
	--	1	2	7	10
total		16	19	13	48

+ evident effect ± dubious effect -- no effect

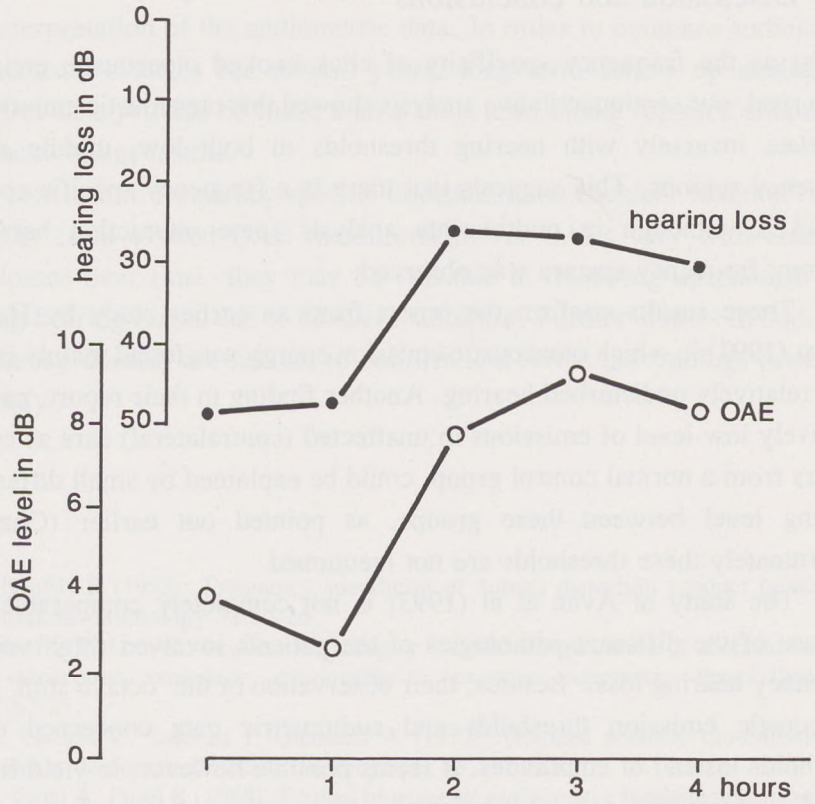


Figure 7.2
Prime example of a positive glycerol test: the mean hearing loss (MFA in dB) improves clearly after 1.5 hours, which is perfectly reflected in an increase in otoacoustic emissions amplitude (OAE in dB SPL). Note the close correlation in time course of the two parameters.

hearing after 1-1.5 hours, followed by a marked deterioration.

In the patients that did not show a positive glycerol effect according to the above-mentioned criteria, hearing levels were generally poorer than in those that did indeed show an improvement in hearing after glycerol ingestion. Analysis of variance with repeated measures of the audiometric data revealed an initial deterioration of hearing in most of these (glycerol negative) patients in the first two hours after glycerol ingestion.

Of the side-effects of glycerol ingestion, a moderate headache was noticed in some patients. Remarkably, one patient with a positive glycerol response (in both OAE and PTA) also noted a complete remission of his tinnitus in the affected ear.

7.4 Discussion and conclusions

As far as the frequency specificity of click evoked otoacoustic emissions is concerned, our semiquantitative analysis showed that otoacoustic emission levels correlate inversely with hearing thresholds in both low, middle and high frequency regions. This suggests that there is a frequency specific component to OAEs, although in multivariate analysis some interaction between the different frequency spectra was observed.

These results confirm the report from an earlier study by Harris and Probst (1992) in which otoacoustic emission energy was found mainly in regions with relatively undisturbed hearing. Another finding in their report, namely the relatively low level of emissions in unaffected (contralateral) ears as compared to ears from a normal control group, could be explained by small differences in hearing level between these groups, as pointed out earlier (Chapter 3): unfortunately these thresholds are not mentioned.

The study of Avan et al (1993) is not completely comparable to ours because of the different pathologies of the patients involved (high versus low freqeuncy hearing loss). Besides, their observation of the 'octave shift' between otoacoustic emission thresholds and audiometric data concerned detection thresholds instead of amplitudes. It seems possible however, to yield frequency specific information on cochlear function by means of click evoked otoacoustic emissions.

In an attempt to assess the possibility to use otoacoustic emissions for follow up purposes, the effects of glycerol on hearing thresholds and click

evoked otoacoustic emissions were evaluated in 30 Menière patients. There was a large variability of the different responses, which called for careful interpretation of the results. This variability may in part be caused by patient factors. In about a third of our cases (21/48), a positive glycerol effect was observed. This is comparable to the report from Bonfils et al (1988). More important, we found a similar effect of glycerol on both hearing and otoacoustic emissions in the majority of cases (30/48). Thus, it seems that audiometric changes are generally parallelled by changes in the level of click evoked otoacoustic emissions.

In one case a seemingly opposite effect was found. Closer inspection of the data revealed that this was probably due to a learning effect rather than a glycerol effect, the patient being difficult to measure audiometrically. Thus, otoacoustic emissions provided additional information which led to a more careful interpretation of the audiometric data. In order to compare audiometric and otoacoustic changes for several years, long term follow up studies are needed. Our data provide no more than a short term model for such studies, be it with encouraging results.

In conclusion: frequency specific information on cochlear function can be obtained by click evoked OAE measurement. As OAEs vary with changing hearing losses over time, they may be valuable in following up patients with fluctuating hearing losses due to Menière's disease. Further studies in both time and frequency domain are needed to confirm and refine the findings presented in this study.

References

Avan P, Bonfils P (1993): Frequency specificity of human distortion product otoacoustic emissions. Audiology 32:12-26

Avan P, Bonfils P, Loth D, Teyssou M, Menguy C (1993): Exploration of cochlear function by otoacoustic emissions: relationship to pure-tone audiometry. Progr Brain Res 97:67-75

Bartoli R, Galizia R, Salonna I, Quaranta A (1992): (Evoked acoustic oto-emissions in cochlear deafness). Boll Soc Ital Biol Sper 68:217-225

Bonfils P, Uziel A, Pujol R (1988): Evoked otoacoustic emissions: a fundamental and clinical survey. ORL J Otorhinolaryngol Relat Spec 50:212-218

Deelen GW van (1986): Studies on cochlear endolymphatic hydrops and Menière's disease. Thesis, Utrecht. 1-96

Fleiss JL (1981): Statistical methods for rates and proportions. Wiley, New York

Gorga MP, Neely ST, Bergman BM, Beauchaine KL, Kaminski JR, Peters J, Schulte L, Jesteadt W (1993): A comparison of transient-evoked and distortion product otoacoustic emissions in normal-hearing and hearing-impaired subjects. J Acoust Soc Am 94(5):2639-48

Hall JW3d, Bratt GW, Schwaber MK, Baer JE (1993): Dynamic sensorineural hearing loss: implications for audiologists; case reports. J Am Acad Audiol 4(6):399-411

Hallpike CS, Cairns H (1938): Observations on the pathology of Ménière's syndrome. J Laryngol Otol 53:625-655

Harris FP, Probst R (1992): Transiently evoked otoacoustic emissions in patients with Meniere's disease. Acta Otolaryngol 112:36-44

Horner K, Cazals Y (1989): Distortion products in early stage experimental hydrops in the guinea pig. Hear Res 43:71-79

Huffelen W van, Mateijsen NJM, Wit HP (1995): Otoacoustic emissions in patients with Menière's disease. Proc 16th Danavox Symp Menière's disease. Kolding, Denmark

Kemp DT, Ryan S, Bray P (1990): A guide to the effective use of otoacoustic emissions. Ear Hear 11:93-105

Klockhoff I, Lindblom U (1966): Endolymphatic hydrops revealed by glycerol test. Acta Otolaryngol 61:459-462

Lind O, Randa J (1989): Evoked acoustic emissions in high-frequency vs. low/medium-frequency hearing loss. Scand Audiol 18:21-25

Lonsbury Martin BL, Harris FP, Stagner BB, Hawkins MD, Martin GK (1990): Distortion product emissions in humans. I. Basic properties in normally hearing subjects. Ann Otol Rhinol Laryngol Suppl 147:3-14

Menière P (1861): Maladies de l'oreille interne offrant les symptômes de la congestion cérébrale apoplectiforme. Gaz Med de Paris 16:88-89

Schmidt JTh, Huizing EH (1992): The clinical drug trial in Menière's disease, with emphasis on the effect of betahistine SR. Acta Otolaryngol Suppl 497:1-189

Wit HP, Langevoort JC, Ritsma RJ (1981): Frequency spectra of cochlear acoustic emissions ("Kemp-echoes"). J Acoust Soc Am 70(2):437-445

▸ 8 ARE TINNITUS AND OTOACOUSTIC EMISSIONS RELATED?

8.1 Introduction

The common sensation of 'tinnitus' comprises a group of symptoms that can cause considerable discomfort to sufferers. In 1981, the participants in the symposium on tinnitus organized by the Ciba Foundation proposed the following definition (Anon 1981a): 'Tinnitus is defined as the sensation of sound not brought about by simultaneously applied mechano-acoustic or electrical signals'. Although admirably brief, this definition unfortunately excludes certain auditory sensations that sometimes clinically present as tinnitus, like pulsatile vascular sounds, myoclonic clicks, etc. Nonetheless, it should be emphasized that tinnitus refers to a sensation and not to any externally detectable correlates. Therefore, the term 'objective tinnitus' was regarded as a misnomer.

The relationship between tinnitus and otoacoustic emissions has been subject of debate and research for a long time (e.g. Gold 1948, Kemp 1981, Wilson 1980,1986, Hazell 1984, Penner 1990,1992, Plinkert et al 1990). It has been shown that a number of drugs can affect both otoacoustic emissions (of different types) and tinnitus alike (Kemp 1978, Johnsen et al 1982, McFadden and Plattsmier 1984, Kollmeier and Uppenkamp 1989, Penner 1989, Haginomori et al 1995). From a clinical point of view, it would be valuable to be able to measure tinnitus objectively. This could be of importance to reassure the patient, and to monitor the effect of therapy. Unfortunately, there seems to be no clear correlation between (different types of) otoacoustic emissions and tinnitus, as may appear from the following review.

In his famous paper on the possibly active elements in the cochlea, Gold (1948) supposed that it must be possible to pick up oscillations originating from the cochlea in the external ear canal. He considered these a likely cause of 'ringing of the ear'. Indeed, after Kemp (1978) demonstrated the existence of these sounds, their relation with subjectively audible tinnitus was investigated in more detail (Wilson 1979, Kemp 1981). It was shown that a sensation of beating could be induced between the "spontaneous narrow-band vibrations" in the ear and an external stimulus of similar frequency. Also, the tinnitus was readily masked by sounds of similar pitch. Remarkably, the external level of the sound did not directly indicate the audibility of the cochlear vibrations: out of five ears with spontaneous mechanical activity, two never exhibited tinnitus.

A similar lack of correlation between subjective (internal) and objective

(external) sound level was reported earlier by others for ears with extremely loud "objective tinnitus" (Glanville et al 1971, Huizing and Spoor 1973). The influence of body position on the 'tinnitus' was thought to point to a vascular origin of the sound. When tilting the head down during anesthesia, the externally audible sound disappeared. However, Wilson (1980) found exactly the opposite: he never found tinnitus in the upright position, whereas in the inverted position, a continuous tonal sensation could be repeatably elicited at 705 Hz in one subject. This coincided with an inversion of the peaks and valleys of the fine-structure of the audiogram and changes (diminutions) in the tone-burst evoked acoustic responses. He supposed that changes in acoustic impedance of the middle ear could induce this effect. Johnsen and Elberling (1982) studying the effect of posture (upright or recumbent) on click evoked otoacoustic emissions, did not notice any such influence in normal subjects. No mention is made of possible tinnitus in their study.

Interesting results were reported by Schloth and Zwicker (1983). By applying changes in air pressure in the external ear canal, a reversible tonal tinnitus became audible in all subjects, which showed a close pitch match to the frequency of the (spontaneous) emissions measured under that pressure condition. This led them to the hypothesis that a continuous emission does not produce a sensation because of adaptation and that a sensation is created only in the non-adapted situation. In his extensive review on tinnitus and its management, Coles (1987) discerns physiological (undisturbing) from pathophysiological (temporary) and pathological (permanent or 'clinical') tinnitus, with further subdivisions according to presumed site of origin.

If a cochlear mechanism is suspected as the cause of the tinnitus, a correlation with (spontaneous) otoacoustic emissions can be expected. However, the results of several clinical studies have not been very conclusive in this respect. There are some reports of a very low correlation between the incidence and frequency of spontaneous otoacoustic emissions and tinnitus (of sensorineural origin) in normal and abnormal ears (Zurek 1981, Tyler and Conrad-Armes 1982, Hazell 1984). In a study on 96 cases, Penner (1990) could attribute spontaneous otoacoustic emissions as a cause to the tinnitus in only 4 cases (95% confidence interval 1-9%). However, it appeared that in a lot of these patients, noise trauma had occurred. Unfortunately, no audiometric thresholds were given. In a later study (Penner and Glotzbach 1994), a

covariation of tinnitus pitch and spontaneous otoacoustic emission was reported, though the observed deviations were indeed very small (±0.5%) and may therefore be attributable to measurement instabilities. In a case report, Plinkert et al (1990) described the possibility to simultaneously suppress both tinnitus and spontaneous otoacoustic emissions in both ears of the same patient, by applying sinusoidal tones from 0.8 to 2 kHz at 25 dB (HL?). This, in their opinion, should prove evidence of active outer hair cell movements as common origin. The audiogram of this patient showed a perceptive loss at 4 kHz for both ears, although no details on noise exposure were given.

This brings us to the clinical fact that (subjectively bothering) tinnitus more often than not is associated with some degree of hearing loss. Surprisingly, little attention has been paid to this phenomenon in the studies mentioned above. Nonetheless, we feel this is an omission, as the inverse relation between (spontaneous) otoacoustic emissions and hearing loss is now well recognized (e.g. Kemp 1978, Schloth 1983, Bonfils 1989). Also, a positive correlation between the level of spontaneous and evoked otoacoustic emissions has been demonstrated (Zwicker and Schloth 1984, Probst et al 1986). In a recent review, however, Josifovic Ceranic et al (1995) stated that there are insufficient data available to come to a firm conclusion regarding the utility of transient evoked emissions in subjects with tinnitus.

In order to adequately judge the value of click evoked otoacoustic emissions in patients with tinnitus, measurements in both tinnitus and non-tinnitus patients should be compared. However, it is impossible to compose the right control group as it is unknown what matching parameters are important (audiological and psychological). Therefore, in this study we investigated the relationship between click evoked otoacoustic emissions and tinnitus in tinnitus patients only, taking into consideration the amount of sensorineural hearing loss in the involved ears. Specifically, we sought to answer the question whether the subjectively experienced sensation level of the tinnitus could be correlated with the level of the otoacoustic emissions.

8.2 Subjects and methods

In the studied population of 500 patients and controls, 168 subjects reported to have some degree of tinnitus, when specifically asked for. Only in 80 patients, this sensation was troublesome and constant ('clinical tinnitus' according to

Coles (1987)), allowing further exploration. A medical and otological history was taken and pure tone audiometry was performed. Click evoked otoacoustic emissions were measured using the ILO88 system with nonlinear clicks. For a more elaborate description of system, set-up and procedures, we refer to Chapter 2. Frequency (pitch, in Hz) and loudness (level, in dB HL) of the tinnitus were matched in the contralateral ear. Either pure tones or narrow band noise were presented intermittently to get the closest match to the patient's experience. In some cases, masking thresholds of the tinnitus were also assessed. The mean hearing threshold was computed by taking the average thresholds at 0.5, 1, 2 and 4 kHz (MFA, Mid Frequency Average), as a measure of overall hearing loss. If necessary, the hearing threshold was interpolated to get an approximate level at the frequency of the tinnitus. This threshold (in the contralateral ear) was then subtracted from the experienced level of the contralaterally matched tinnitus, to yield the 'tinnitus sensation level' expressed in dB SL.

This matched loudness value of tinnitus in dB SL is not an exact measurement of the subjective loudness of the tinnitus (Anon 1981b), but it is the closest parameter we can get in order to compare data across patients with varying degrees of hearing loss. The problem lies in the fact that it is practically impossible to perform an exact measurement of subjective loudness sensation, due to the diminished dynamic range of the affected ears. In other words: a stimulus of 10 dB above hearing threshold may seem louder in a diseased ear than in a normal ear. At present, no practically applicable method seems available to circumvent this pitfall. A similar problem is constituted by the fact that the nature of the tinnitus sometimes best matches narrowband noise instead of pure tones, and that its frequency may exceed the upper limit of the OAE measurement spectrum (6 kHz).

The otoacoustic emission parameters studied were the overall response level ('wideband OAE') and the (approximate) level of the otoacoustic emissions at the frequency of the tinnitus ('narrowband OAE'). This was computed by multiplying the visually scored spectral content of the response (0, 1 or 2, as explained in Chapter 2.3.3) in the region of the tinnitus with the overall otoacoustic emission level (ECHO). Taking into consideration the frequency specificity of both the evoked otoacoustic emission response and the tinnitus, we investigated the relation between the hearing loss at the (approximate) frequency

of the tinnitus, its 'sensation level' and the otoacoustic emission response (both wideband and narrowband OAE).

Statistical analysis was performed using the SPSS/PC+ package, by making correlation/regression plots for hearing thresholds, tinnitus level and otoacoustic response, as described above. Furthermore, multiple regression analysis was performed to adjust for the confounding influence of hearing loss.

8.3 Results

The 80 persons reporting persistent tinnitus had a mean age of 50 ± 14 years (normal distribution), and a median midfrequency hearing threshold (MFA) of 28 and 23 dB HL (range 0-125 and 5-85 dB) for right and left ears, respectively (non-normal distribution). The tinnitus was unilateral in 59 cases (in 37 cases in the right ear, in 22 cases in the left ear); in 21 cases it was bilateral.

The distribution of frequency and loudness of the tinnitus for right and left ears is shown in Figure 8.1. The mean (contralaterally judged) loudness was 48 ± 25 dB HL and 43 ± 23 dB HL for right and left ears, respectively, with an appoximately normal distribution. In contrast, the frequency of the reported tinnitus showed a random pattern of distribution, ranging from 125 to 12,000 Hz (right) and 250 to 11,000 Hz (left). There appeared to be no significant correlation between the loudness and the frequency of the tinnitus, as illustrated in Figure 8.2.

Tinnitus loudness did correlate, however, with the overall hearing loss as expressed by the MFA ($r = 0.51$ and 0.44 for right and left ears; $p < .005$ for both), as displayed in Figure 8.3. As it is known that there is a negative correlation between hearing threshold and click evoked otoacoustic emission level (see previous Chapters), we were not surprised to find a similarly negative correlation between otoacoustic emission level (OAE in dB SPL) and tinnitus level (in dB HL). In Figure 8.4 these parameters were plotted. It is apparent that with increasing tinnitus levels, the otoacoustic emissions diminish for both right and left ears ($r = -.33$ and $-.36$, respectively; $p < .05$). This was due to the hearing loss as third factor significantly influencing both the otoacoustic emission level and the tinnitus loudness, as confirmed by multiple regression analysis ($r = -.678$ and $+.537$ respectively).

To compensate for the hearing loss factor, we investigated the 'sensation

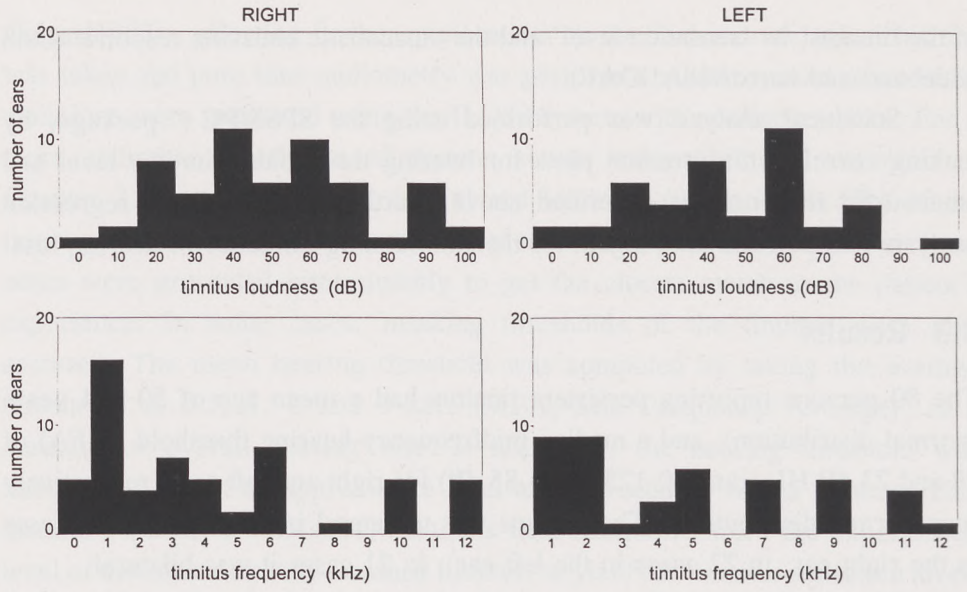


Figure 8.1
Distribution of loudness (dB HL) and frequency (Hz) of tinnitus in right ears (n=58) and left ears (n=43). The loudness of the tinnitus shows an approximately normal distribution; its (approximate) frequencies are randomly distributed.

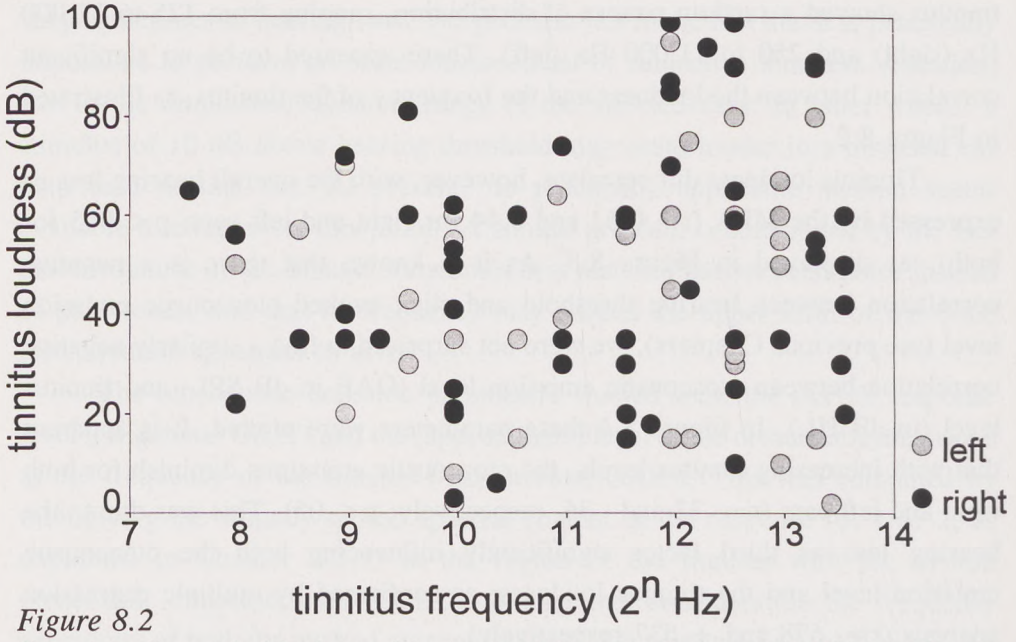


Figure 8.2
Contralaterally matched loudness of tinnitus (dB HL) and its frequency (in 2^n Hz) in 58 right and 43 left ears: there is a very small positive correlation between these parameters which is not statistically significant ($p > .05$).

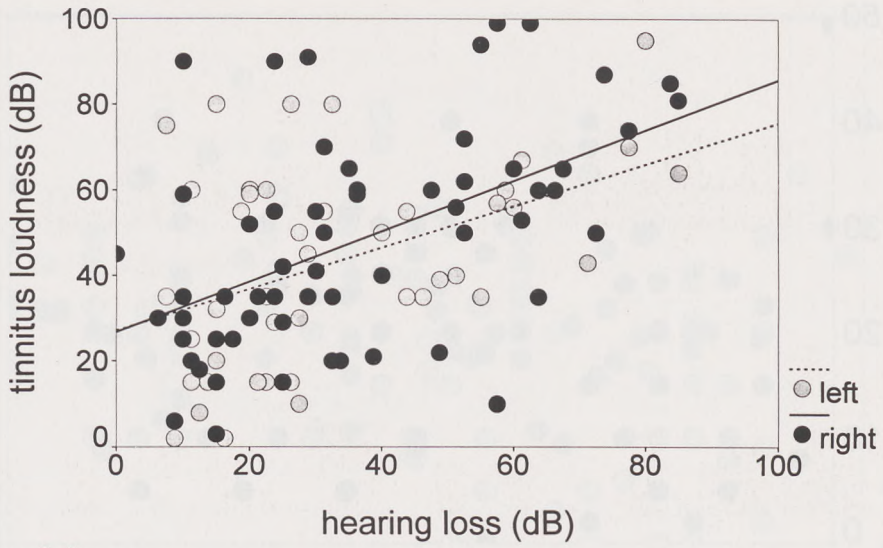


Figure 8.3
Tinnitus loudness level (dB HL) and mean hearing thresholds (MFA in dB HL) for right (n=58) and left (n=43) ears. There is a significant positive correlation (r=.51 and .44; p<.005), indicating that a larger hearing loss coincides with a higher tinnitus loudness level.

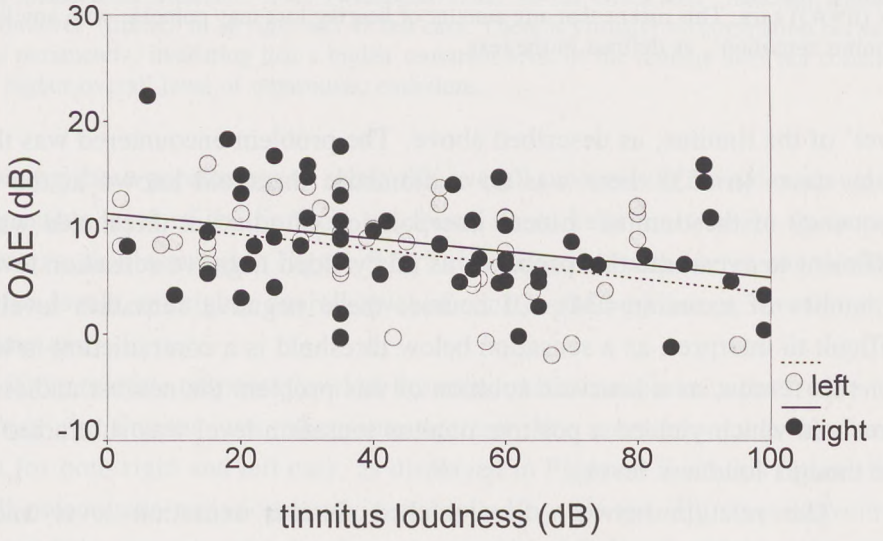


Figure 8.4
Otoacoustic emission level (OAE in dB SPL) and tinnitus loudness (dB HL) in 58 right and 43 left ears. There is a statistically significant negative correlation (r=-.33 and -.36; p<.05) which means that higher tinnitus loudness levels coincide with lower otoacoustic emission levels. This can be explained by a third factor: overall hearing loss.

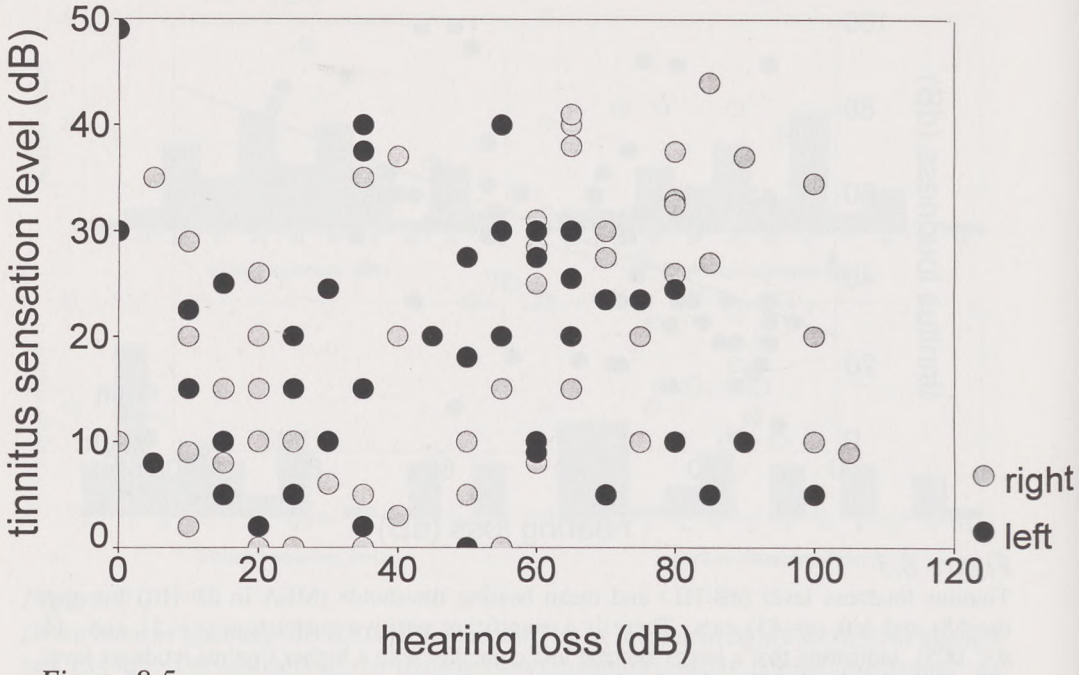


Figure 8.5
Matched 'tinnitus sensation level' (dB SL) and concomitant hearing loss (dB) at the approximate tinnitus frequency: there is no significant correlation for both right (n=58) and left (n=43) ears. This means that any amount of hearing loss may coincide with any level of 'tinnitus sensation', as defined in the text.

level' of the tinnitus, as described above. The problem encountered was that in many cases (n=53) there was no audiometric threshold known at the exact frequency of the tinnitus. Linear interpolation of adjacent thresholds was not sufficient to overcome this problem, as this yielded negative sensation levels in a number of cases (n=34). Of course, these negative sensation levels are difficult to interpret, as a sensation below threshold is a contradiction in terms. For this reason, as a heuristic solution of this problem the nearest audiometric threshold which yielded a positive tinnitus sensation level was subtracted from the tinnitus loudness level.

The relation between the matched tinnitus sensation level and the (approximate) hearing threshold at the frequency of the tinnitus was displayed in Figure 8.5. There was no significant correlation between these two parameters. This indicates that the amount of hearing loss did not influence the sensation level of the tinnitus.

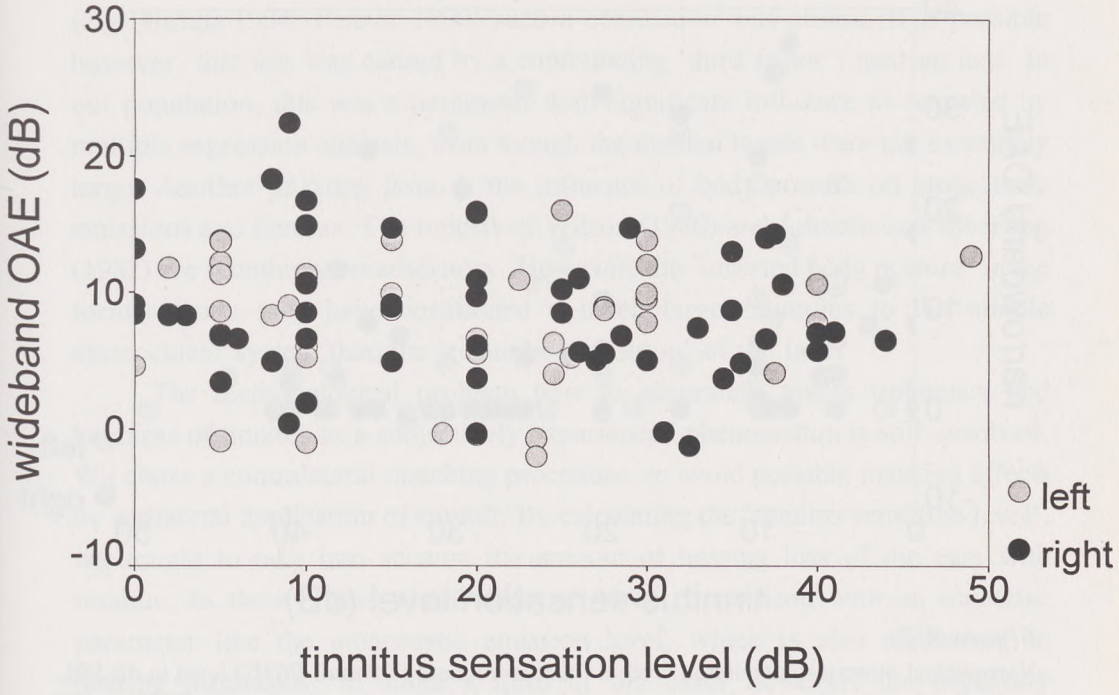


Figure 8.6
Overall otoacoustic emission level (wideband OAE in dB SPL) and 'matched tinnitus sensation level' (dB SL) in 58 right and 43 left ears. There is virtually no correlation between the two parameters, indicating that a higher sensation level of the tinnitus does not coincide with a higher overall level of otoacoustic emissions.

Combining these parameters to relate the overall otoacoustic emissions level to the sensation level of the tinnitus, we found no correlation between these two parameters, as illustrated in Figure 8.6. This means that with increasing tinnitus sensation levels, no higher overall level of click evoked emissions was found in the same ear.

If the relative response level of the otoacoustic emissions in the frequency region of the tinnitus was taken into account, the correlation was similarly absent for both right and left ears, as displayed in Figure 8.7. In this figure, the overall otoacoustic emission level is multiplied by the visually scored spectral content of the response in the frequency region of the tinnitus to yield the 'narrowband OAE'. It is obvious that any amount of frequency specific otoacoustic emission response may coincide with a given tinnitus sensation level.

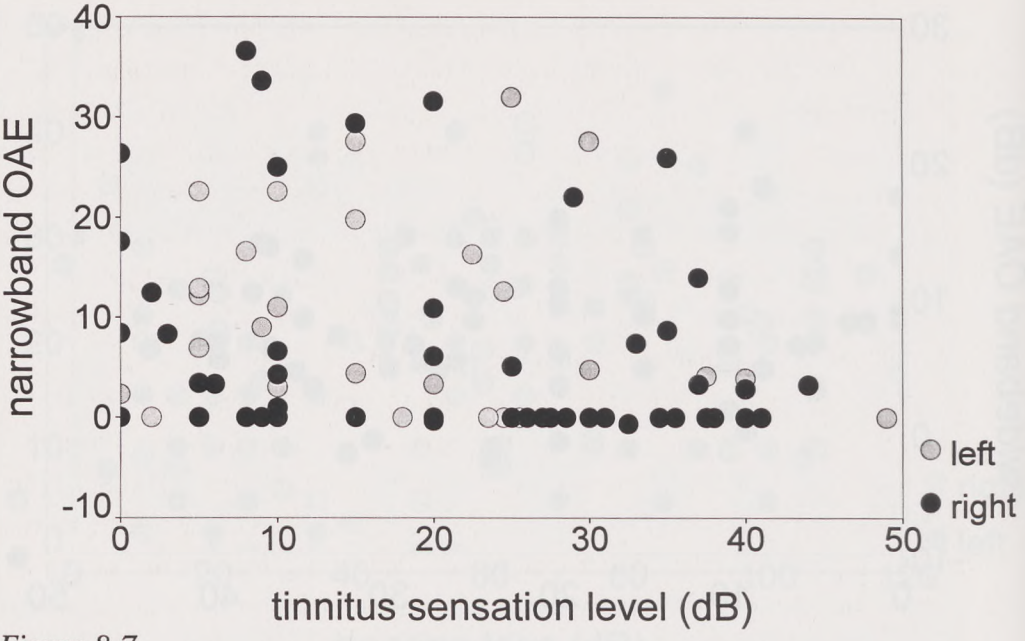


Figure 8.7
Narrowband otoacoustic emission level at tinnitus frequency (overall ECHO level in dB SPL multiplied by visually scored response) and 'matched tinnitus sensation level' (dB SL) in 58 right and 43 left ears. There is no significant positive correlation for both right and left ears. This means that any sensation level of the tinnitus may coincide with any level of emissions in the frequency region of the tinnitus.

8.4 Discussion and conclusions

The sensation of tinnitus is often found in patients with some degree of hearing loss. Its clinical relevance depends on the amount of disturbance caused to the patient: this can be considerable, though sometimes it is only experienced as a concomitant symptom to the socially more invalidating hearing loss. In our population, the prevalence of permanent ('clinical') tinnitus was 16% (80/500), which is comparable to that reported in the literature (Coles 1984, MRC Institute of Hearing Research 1987).

Though the exact mechanisms of tinnitus generation are still unclear, cochlear dysfunction is involved in most cases (Coles 1987). The reports on the interaction between spontaneous otoacoustic emissions and tinnitus show that there may be a correlation as demonstrated by their suppressability in certain cases (e.g. Plinkert et al 1990), though in larger studies with a different set-up

(e.g. Hazell 1984, Penner 1990) such a correlation was absent. It is possible however, that this was caused by a confounding 'third factor': hearing loss. In our population, this was a parameter with significant influence as revealed by multiple regression analysis, even though the median losses were not extremely large. Another puzzling issue is the influence of body posture on otoacoustic emissions and tinnitus. The reports of Wilson (1980) and Johnsen and Elberling (1982) are seemingly contradictory. However, the 'inverted body posture' in the former study may have constituted a much larger stimulus to the middle ear/cochlear system than the 'recumbent position' of the latter.

The methodological problem how to accurately assess frequency and loudness of tinnitus as a subjectively experienced phenomenon is still unsolved. We chose a contralateral matching procedure, to avoid possible masking effects by ipsilateral application of stimuli. By calculating the 'tinnitus sensation level', we sought to take into account the amount of hearing loss of the ears with tinnitus. In theory, this would allow a fairer comparison with an objective parameter like the otoacoustic emission level, which is also dependent on hearing thresholds. In about a third of the cases however, the necessary interpolations of the procedure would lead to negative sensation levels. Therefore, in these cases a different calculation was performed to compensate for this intrinsic contradiction.

It should be emphasized that the tinnitus sensation level is not an exact measure of the subjective loudness, due to the often diminished dynamic range of the affected ear. It seems very difficult to compensate for this distorting factor: no practically applicable method seems available to perform such a correction. A similar problem is encountered in the frequency matching procedures, reducing the validity of the data. It was shown by Dauman and Cazals (1989) that psychoacoustic tuning curves from ears with hearing loss and tinnitus revealed a diminished frequency selectivity. An exact tinnitus pitch match is therefore difficult to obtain from such ears.

To our knowledge, this is the first large-scale study on the correlation between click evoked otoacoustic emissions and tinnitus, in which the hearing loss of the ears is also taken into account. The fact that no significant correlations were found between click evoked otoacoustic emission level and tinnitus sensation level, may have been due to the methodological problems described above. It is important to realize that although no statistically

significant correlation seems to exist, a causal relationship between spontaneous OAEs and tinnitus may be found in individual cases (Penner 1990). So far, the assumption that OAEs may give rise to tinnitus remains sheer speculation.

In order to confirm these results, more elaborate data from both tinnitus and non-tinnitus patients would be valuable, especially with respect to the spectral weighing of the response and possibly the inclusion of spontaneous and distortion product emissions into the analysis. Also, it would be interesting to measure emissions in higher frequency ranges (the present equipment range extends to 6 kHz only), as the reported tinnitus frequency sometimes exceeds the limitations of the measurement system. If possible, the methodological problem of the exact assessment of the subjectively experienced loudness could be solved by measuring isofone curves for all affected ears, from which 'corrected sensation levels' could then be deduced.

In conclusion: the outcome of this study showed that there is no significant correlation between the 'tinnitus sensation level' as an approximate measure of the loudness of the tinnitus as experienced by the patient and the click evoked otoacoustic emission level as measured by the researcher. Therefore, an 'objective tinnitus measurement' as originally supposed by Gold (1948) does not seem to be possible by using click evoked otoacoustic emissions. However, this puzzling issue deserves further study because of its potential benefits to many sufferers around the world.

References

Anon (1981a): Definition and classification of tinnitus. In: Evered D, Lawrenson G (eds) Tinnitus: Ciba Foundation Symposium 85, app I, 300-302. London, Pitman

Anon (1981b): Guidelines for recommended procedures in tinnitus testing. In: Evered D, Lawrenson G (eds) Tinnitus: Ciba Foundation Symposium 85, app II, 303-306. London, Pitman

Bonfils P (1989): Spontaneous otoacoustic emissions: clinical interest. Laryngoscope 99:752-756

Coles RRA (1987): Tinnitus and its management. In: Kerr AG et al (eds) Scott-Brown's Otolaryngology Vol 2. Adult audiology p368-414

Coles RRA (1984): Epidemiology of tinnitus: (1) prevalence. J Laryngol Otol Suppl 9:7-15.

Dauman R, Cazals Y (1989): Auditory frequency selectivity and tinnitus. Arch Otorhinolaryngol 246(5):252-5

Glanville JD, Coles RRA, Sullivan BM (1971): A family with objective high-tonal tinnitus. J Laryngol Otol 85:1-10.

Gold T (1948): Hearing II. The physical basis of the action of the cochlea. Proc Roy Soc B 135:492-498

Haginomori S, Makimoto K, Araki M et al (1995): Effect of lidocaine injection on EOAE in patients with tinnitus. Acta Otolaryngol 115(4):488-492

Hazell JWP (1984): Spontaneous cochlear acoustic emissions and tinnitus. Clinical experience in the tinnitus patient. J Laryngol Otol Suppl 9:106-110

Huizing EH, Spoor A (1973): An unusual type of tinnitus. Arch Otolaryngol 98:134-136

Johnsen NJ, Elberling C (1982): Evoked acoustic emissions from the human ear II: normative data in young adults and influence of posture. Scand Audiol 11:69-77

Josifovic Ceranic B, Prasher DK, Luxon LM (1995): Tinnitus and otoacoustic emissions. Clin Otolaryngol 20:192-200

Kemp DT (1978): Stimulated emissions from within the human auditory system. J Acoust Soc Am 64(5):1386-1391

Kemp DT (1981): Physiologically active cochlear micromechanics - one source of tinnitus. In: Tinnitus, p 54-81. London, Pitman Books Ltd.

Kollmeier B, Uppenkamp S (1989): Analysis and influence of lidocaine on evoked otoacoustic emissions from tinnitus sufferers. In: Wilson JP,Kemp DT (eds) Cochlear mechanisms. Structure, function and models, p 331-339. New York, Plenum.

McFadden D, Plattsmier HS (1984): Aspirin abolishes spontaneous oto-acoustic emissions. J Acoust Soc Am 76:443-448

MRC Institute of Hearing Research (1987): Epidemiology of tinnitus in adults. In: Hazell JWP (ed) Tinnitus, Ch 3. Edinburgh, Churchill Livingstone

Penner MJ (1989): Aspirin abolishes tinnitus caused by spontaneous otoacoustic emissions. A case study. Arch Otolaryngol Head Neck Surg 115:871-875

Penner MJ (1990): An estimate of the prevalence of tinnitus caused by spontaneous otoacoustic emissions. Arch Otolaryngol Head Neck Surg 116:418-423

Penner MJ (1992): Linking spontaneous otoacoustic emissions and tinnitus. Br J Audiol 26:115-123

Penner MJ, Glotzbach L (1994): Covariation of tinnitus pitch and the associated emission: a case study. Otolaryngol Head Neck Surg 110:304-309

Plinkert PK, Gitter AH, Zenner HP (1990): Tinnitus associated spontaneous otoacoustic emissions. Active outer hair cell movements as common origin? Acta Otolaryngol 110:342-347

Probst R, Coats AC, Martin GK, Lonsbury Martin BL (1986): Spontaneous, click-, and toneburst-evoked otoacoustic emissions from normal ears. Hear Res 21:261-275

Schloth E, Zwicker E (1983): Mechanical and acoustical influences on spontaneous oto-acoustic emissions. Hear Res 11:285-293

Tyler RS, Conrad-Armes D (1982): Spontaneous acoustic cochlear emissions and sensorineural tinnitus. Br J Audiol 16:193-4

Wilson JP (1979): Recording of the Kemp echo and tinnitus from the ear canal without averaging. Proc Physiol Soc 19(2):8-9

Wilson JP (1980): Evidence for a cochlear origin for acoustic re-emissions, threshold fine-structure and tonal tinnitus. Hear Res 2:233-252

Wilson JP (1986): Otoacoustic emissions and tinnitus. Scand Audiol Suppl 25:109-119

Zurek PM (1981): Spontaneous narrow-band acoustic signals emitted by human ears. J Acoust Soc Am 69:514-523

Zwicker E, Schloth E (1984): Interrelation of different oto-acoustic emissions. J Acoust Soc Am 75:1148-1154

▸ 9 SUMMARY AND CONCLUSIONS

1. This thesis deals with the application of otoacoustic emissions (OAEs) in clinical practice. The classical way of hearing assessment has always been by pure tone audiometry. The tremendous dynamic range of the auditory system in combination with its high frequency resolution properties, gave rise to the idea that an active mechanism must be involved in the processing of sound by the inner ear (Gold 1948). This positive feedback mechanism would cause the ear to ring by itself, and to emit sounds.

The actual discovery of these emitted sounds, nowadays called otoacoustic emissions, marked a change in both experimental and clinical audiology (Kemp 1978). The inner ear is indeed no longer considered a passive system, but a highly tuned active generator of sounds, at least in normal situations. When the ear is damaged, the OAEs disappear. The OAEs may occur spontaneously, but also in response to clicks, tone-bursts or other stimuli. The various ways of eliciting OAEs have different practical application possibilities. We intended to investigate the clinical value of click evoked OAE measurements in daily practice, as compared to the pure tone audiogram.

2. At the Utrecht University Hospital, a total number of 500 normal hearing and hearing impaired subjects were tested by conventional audiometry as well as OAE measurements. The data comprised a wide range of diagnoses, ages and hearing losses. Classification criteria, measurement procedures and statistical methods were described. Careful analysis of the results in 1000 ears was performed to get insight into the complex interrelation of the parameters influencing both kinds of measurements. Although it proved relatively easy to obtain adequate audiometric and otoacoustic data, the interpretation of the data required significant prudence.

3. The results of the control group of 122 normal ears not only confirmed the general experience with OAE assessment as being easy, quick and objective, but also showed features not previously reported. A statistically significant correlation was found between mid frequency hearing threshold and OAE level. By calculating regression lines from these ears with virtually no hearing loss, the disappearance of OAE responses with increasing thresholds could be adequately deduced. Also, an asymmetry was noted in the correlation between OAEs and hearing thresholds, possibly due to efferent influences. Though

audiometrically similar, female ears compared favourably to male ears with respect to their OAEs, as did right ears compared to left. In conclusion: OAE measurements in normal ears showed clinically relevant features, with implications for practical application (for example in screening).

4. The influence of middle ear function on click evoked OAEs was found not to exceed that of the cochlea, as opposed to suggestions in the literature. A double impact of middle ear dysfunction on OAEs has been hypothesized as both stimulus and response are diminished. Apparently, our data represent the first large-scale study on OAEs in adults with varying degrees of conductive hearing loss. However, detailed analysis of OAE parameters in groups of ears with mixed conductive and sensorineural losses failed to reveal significant differences, indicative of such a two-fold influence. Consequently, the hypothesis that the cochlea and the middle ear system are equally important to the subsistence of OAEs could not be rejected.

5. It is generally acknowledged that after the neonatal period, the level of OAE responses diminishes with age. Surprisingly, this is often attributed to an "age effect", overlooking possible hearing loss as an important third factor. In our study comparing large groups of ears with equal losses across various ages, no differences in OAE levels were found. Moreover, multiple regression analysis of hearing loss with the OAE level as dependent variable in 975 ears showed that only 0.5% of the OAE variability was explained by the age factor, as opposed to 52.5% by the hearing loss factor. Consequently, we concluded that the so-called "age effect" has no clinical relevance.

6. In differential diagnosis, OAE measurements have the theoretical advantage of being objective and sensitive. In 192 ears we examined the possibility to discriminate between presbycusis and noise induced hearing loss, but found no significant differences. However, in 41 ears with suspected psychogenic hearing loss an almost normal level and reproducibility of OAEs was found, in contrast to the low level of OAEs in a matched control group of ears with real hearing losses. Thus, OAE measurement may be helpful in uncovering psychogenic hearing loss, though not in differentiating between presbycusis and noise induced hearing loss.

7. The frequency specificity of OAEs and their behavior with fluctuating hearing loss was studied in 30 patients with Menière's disease, comparing audiometric with otoacoustic parameters. Glycerol induced changes were used as a model for long term fluctuations. In all frequency regions (0.5 - 4 kHz), the ears with OAEs showed better hearing thresholds than the ears without OAEs. These differences were statistically significant, though some interaction between the frequency spectra was noted. The short term effect of glycerol on OAE level and hearing threshold was similar in the majority of ears (30/48). We concluded that OAE measurement may yield frequency specific information on cochlear function and that OAEs can be valuable in the follow-up of patients with fluctuating hearing loss.

8. In contrast to the original idea of Gold (1948), the relation between OAEs and 'ringing of the ear' is very intricate. Although many reports on the poor correlation between OAEs and tinnitus exist, the concomitant hearing loss is seldom taken into account. Besides, methodological problems arise when studying the subjective phenomenon of tinnitus. Nonetheless, from a clinical and experimental point of view, an objective measurement of tinnitus is desirable. In 101 ears with persistent tinnitus the hearing loss, OAEs and tinnitus parameters were carefully analysed. This revealed no statistically significant correlation between OAE level and 'tinnitus sensation level' (tinnitus loudness corrected for hearing loss at tinnitus frequency). Thus, it proved not possible to assess this subjective phenomenon by an objective parameter of cochlear function. Nonetheless, the pitfalls related to pure tone audiometry were illustrated by this attempt.

In conclusion, click evoked otoacoustic emission measurement was found to be a valuable diagnostic tool in clinical practice, not replacing but supplementing the pure tone audiogram.

SAMENVATTING EN CONCLUSIES

1. Dit proefschrift behandelt de toepassing van otoakoestische emissies (OAEs) in de (poli)klinische praktijk. De bepaling van de gehoorscherpte geschiedt van oudsher door middel van toonaudiometrie. Het enorme dynamisch bereik van het auditief systeem in combinatie met een verbluffende frequentieselectiviteit, bracht Gold in 1948 reeds op het idee dat er een actief mechanisme betrokken moest zijn bij de verwerking van geluid door het binnenoor. Door deze positieve terugkoppeling zou het oor gaan 'rondzingen' en zo vanzelf geluid kunnen maken. De feitelijke ontdekking van deze geluiden (OAEs) door Kemp in 1978, betekende een ommekeer voor de experimentele en klinische audiologie. Het binnenoor wordt niet meer als een passief systeem beschouwd, maar als een zeer gevoelig, actief geluidgenererend geheel, althans in normale omstandigheden. Bij beschadiging van het gehoor verdwijnen de OAEs. De OAEs kunnen 'spontaan' voorkomen, maar ook als reactie van het oor op kliks, toonstootjes of andere stimuli. De verschillende vormen van stimulatie hebben ook verschillende praktische toepassingsmogelijkheden. Wij hebben getracht de klinische waarde van door kliks opgewekte otoakoestische emissies te bepalen in de dagelijkse praktijk, in vergelijking met het toonaudiogram.

2. In totaal 500 normaalhorende en slechthorende personen werden onderzocht in het Academisch Ziekenhuis Utrecht, middels toonaudiometrie en bepaling van door kliks opgewekte OAEs. De aldus verkregen gegevens omvatten een scala van diagnoses, leeftijden en gehoorverliezen. De verschillende classificatie-criteria, onderzoeksprocedures en statistische methoden werden beschreven. Analyse van de resultaten in 1000 oren leverde inzicht in de complexe samenhangen tussen de parameters die van invloed zijn op beide soorten metingen. Hoewel het relatief eenvoudig bleek om valide audiometrische en otoakoestische gegevens te verkrijgen, was de interpretatie hiervan lastiger.

3. De resultaten van de controlegroep van 122 normale oren bevestigden algemene ervaringen met OAE metingen: ze zijn objectief, snel en betrouwbaar uit te voeren. Ook werden niet eerder gemelde eigenschappen ontdekt. Zo was er een statistisch significante correlatie tussen de gemiddelde gehoordrempel en het niveau van de OAEs. Door hieruit regressielijnen te berekenen kon het verdwijnen van OAEs bij toenemend gehoorverlies adequaat worden voorspeld.

Ook werd een asymmetrie gevonden in de correlaties tussen OAEs en gehoordrempels, mogelijk ten gevolge van efferente invloeden. Hoewel er geen statistisch significante verschillen in gehoordrempels waren, bleken de OAEs wel significant sterker in oren van vrouwen en in rechter oren. Concluderend werden in normale oren met OAE metingen bevindingen gedaan die voor praktische toepassing (bijvoorbeeld screening) consequenties kunnen hebben.

4. De invloed van de functie van het middenoor op door kliks opgewekte OAEs bleek niet sterker dan die van het binnenoor, in tegenstelling tot suggesties uit de literatuur. Een dubbele invloed van middenoordysfunctie is verondersteld, omdat zowel de stimulus als de respons daardoor verminderd zouden worden. De hier gepresenteerde gegevens lijken de eerste grootschalige studie naar OAEs bij volwassenen met verschillende geleidingsverliezen te zijn. Bij analyse van OAE parameters in groepen oren met geleidings- en perceptieverliezen werden geen significante verschillen gevonden die zouden kunnen duiden op een dubbele invloed van het middenoor. Derhalve kan de hypothese dat binnen- en middenoor even belangrijk zijn voor het OAE-niveau niet verworpen worden.

5. Het is algemeen bekend dat na de eerste levensdagen het niveau van de OAEs afneemt met de leeftijd. Dit wordt vaak geweten aan een "leeftijdseffect", waarbij eventueel gehoorverlies als belangrijke factor over het hoofd gezien wordt. In onze studie vergeleken wij grote groepen oren met dezelfde gehoorverliezen over verschillende leeftijden, waarbij geen enkel significant verschil in OAE niveau werd gevonden. Bovendien werd middels multiple regressie-analyse met het OAE niveau als afhankelijke variabele aangetoond dat slechts 0,5% van de variabiliteit in OAEs verklaard werd door de factor leeftijd, tegen 52,5% door de factor gehoorverlies. Concluderend blijkt dat het zogenaamde "leeftijdseffect" geen klinische relevantie heeft.

6. OAE metingen hebben door hun objectiviteit en gevoeligheid een theoretisch voordeel bij diagnostische dilemma's. Wij onderzochten de mogelijkheid om te onderscheiden tussen presbyacusis en lawaaislechthorendheid bij 192 oren. Er werden geen significante verschillen gevonden in OAE sterkte. In 41 gevallen van vermoede psychogene slechthorendheid werd echter een vrijwel normale sterkte en reproduceerbaarheid van OAEs gevonden, in tegenstelling tot de lage

OAE niveau's in een vergelijkbare controlegroep van oren met werkelijke gehoorverliezen. OAE metingen kunnen dus van nut zijn bij het opsporen van psychogene gehoorverliezen, maar niet bij het onderscheiden tussen presbyacusis en lawaaislechthorendheid.

7. De frequentiespecificiteit van OAEs en hun gedrag bij fluctuerend gehoorverlies werd onderzocht bij 30 patiënten met de ziekte van Menière, door het vergelijken van audiometrische en otoakoestische parameters. De kortdurende veranderingen tengevolge van glycerolinname werden gebruikt als model voor langer durende fluctuaties. In alle frequentiebanden (0.5 - 4 kHz) vonden wij in oren met OAEs betere gehoordrempels dan in oren zonder OAEs. Deze verschillen waren statistisch significant, hoewel er enige interactie tussen de spectra bestond. Glycerol had een vergelijkbaar effect op gehoordrempels en OAEs in de meeste gevallen (30/48). Concluderend: meting van OAEs kan frequentiespecifieke informatie over het functioneren van de cochlea opleveren, en van nut zijn bij het vervolgen van patiënten met fluctuerend gehoorverlies.

8. In tegenstelling tot het oorspronkelijke idee van Gold (1948) bestaat er een ingewikkelde relatie tussen OAEs en 'suizen van het oor' (tinnitus). Hoewel er vele onderzoeken bestaan over de slechte correlatie tussen deze twee grootheden, werd het begeleidende gehoorverlies zelden verdisconteerd. Daarnaast zijn er methodologische problemen bij het bestuderen van het subjectieve fenomeen tinnitus. Toch is vanuit klinisch en experimenteel oogpunt een objectieve bepalingsmethode wenselijk. Bij 101 oren met continu oorsuizen werden het gehoorverlies, OAEs en tinnitusparameters geanalyseerd. Dit leverde geen statistisch significante correlaties op tussen OAE niveau en 'tinnitus sensatieniveau' (luidheid gecorrigeerd voor gehoorverlies). Het was dus niet mogelijk om dit subjectieve fenomeen te bepalen met een objectieve parameter van de cochleaire functie. Desniettegenstaande werden de valkuilen van de toonaudiometrie hierdoor opnieuw belicht.

Conclusie: bepaling van door kliks opgewekte otoakoestische emissies bleek een waardevol diagnostisch instrument, niet als vervanging van maar als aanvulling op het toonaudiogram.

Dankwoord

Vele zijn de beproevingen die een promovendus moet doorstaan, maar ook vele zijn de helpende handen die hem overeind houden om het werk te volvoeren. Ik wil dan ook allen die aan dit proefschrift bijdroegen mijn dank betuigen.

Hooggeleerde Huizing, U hebt als promotor en opleider mijn eerste schreden op het pad der wetenschap begeleid en mij steeds gestimuleerd om dit onderzoek af te ronden, al ging het soms door diepe dalen. Hooggeleerde Wit, beste Hero, jij was een uitnemend leermeester, en van jouw opbouwende kritiek heb ik veel geleerd. Het was telkens een genoegen met je te discussiëren over alles wat met horen en OAEs te maken heeft. Hooggeleerde Van den Broek, beste Paul, dank voor alle ruimte die je gaf om mij in en buiten het vak verder te ontplooien. Andries Clemens, jij hebt als eerste mijn interesse voor OAEs gewekt, en stond daarmee als 'coach-promotor' aan de wieg van dit proefschrift. Zonder onze vele vruchtbare discussies had dit werk er heel anders uitgezien. Mijn dank geldt natuurlijk evenzeer de audiologie-assistentes in het AZU, speciaal Willy van Asselt, Francis Visser en Coby Peereboom, die het leeuwedeel van de OAE-metingen verrichtten, met hulp van Remco de Bree en Virjo Braat. Jacques Berk en Rinus de Winter zorgden voor prima technische ondersteuning. En als het toch helemaal mis dreigde te lopen, was er in het lab altijd wel een Tom Poes alias Johan de Groot, Hans van Dijk, Sjaak Klis of Frits Meeuwsen die een list verzon.

Op een misschien minder directe, maar zeker niet minder belangrijke manier hebben vele mede-assistenten en (mede-)stafleden in Utrecht en Nijmegen, en mijn maten in Arnhem, mij geholpen in soms klemmende situaties. Voor jullie steun en flexibiliteit ben ik zeer dankbaar. Bovenal bewaar ik goede herinneringen aan de plezierige samenwerking in allerlei vormen, die als 'peer pleasure' een onmisbare voedingsbodem was om dit boek af te maken.

Ingeborg van der Tweel, jij hebt met veel geduld en vakmanschap gezorgd voor het statistische hoofdwasprogramma, waaruit een frisse kijk op de brei van gegevens ontstond. Many thanks are due to Sara van Wassenaer-Matson, my faithful guide through the jungle of English idiom. In de eindstrijd zorgden Ingrid Janssen, Paul Postmes en Mariëtte Klok voor mooie plaatjes, en Diny Helsper-Peters voor praktische lay-out aanwijzingen.

Veel van mijn vrienden en familieleden hebben zich langdurig vol begrip door mij laten verwaarlozen, waarvoor dank. Speciaal de studieuze gastvrijheid van mijn schoonouders, en de supraparanymphale steun van Thomas Rinne en Maarten Majoor is onvergetelijk. Frau Doktor, lieve Geertruid, het is af....

Curriculum vitae

Auctor dissertationis huius Constantinus Tilanus anno MMDCCXIV a.U.c. Amstelodami natus est. Aetate septendecim educatione secundaria ad finem perducta arti medicinae in urbis illae Universitate Libera studere incepit. Multos annos ita perseveravit, quibus non solum disciplinam augebat, sed etiam artem musicalem exercuit fidicula canens moderansque Orchestram Studiosorum Neerlandicam. Anno MMDCCXXXIX a.U.c. studiis finitis examinibusque ultimis perfectis, discipulum otorhinolaryngologicum eum Ultraiecti Universitatis valetudinarii professor ille illustris Egbertus Huisingis accepit. Quo usus magistro, artem perdidicit. Eodem tempore examinationem otoemissionum acusticarum incipiebat in qua deinde intra muros valetudinarii Universitatis Noviomagi adiuvante professore egregio honestissimoque Paulo Vandenbruco progressus fecit. Doctorandum iam sede collocata ad oram Ueluam in associationem quae actionibus regionem de Aernhemio ad Subenharam cingit, eum Henricus Boelenus, Josephus de Leonibus, Enno Schansius, Eduardus Soudinius Johannesque Vossius in optimam collaborationem acceperunt. Uxor carissima eius magistra iuris Gertrudis de Wassenaria est, eisque tres filiae nominibus Clara, Diede Ottolienque natae sunt.

Levensloop

De auteur van dit proefschrift, Stijn Tilanus, werd op 2 april 1961 geboren te Amsterdam. Na het doorlopen van de middelbare school begon hij in 1978 in diezelfde stad met de studie medicijnen aan de Vrije Universiteit. Gedurende zijn studie deed hij niet alleen medische kennis op, maar was hij ook als (alt)violist actief in het Nederlands Studenten Orkest. Na zijn artsexamen in 1986 werkte hij als assistent KNO-heelkunde in het Academisch Ziekenhuis Utrecht onder leiding van Prof.Dr E.H. Huizing, die hem de kneepjes van het vak leerde. Tijdens zijn opleiding maakte hij een begin met dit onderzoek over otoakoestische emissies. Nadien werkte hij als staflid in het Academisch Ziekenhuis Nijmegen hieraan verder, daarbij ruimhartig gesteund door Prof.Dr P. van den Broek. Aan de Veluwezoom vestigde hij zich vervolgens, opgenomen als lid van de maatschap KNO-Heelkunde Arnhem-Velp-Zevenaar in plezierige samenwerking met Henk Boelen, Jos van Leeuwen, Enno van der Schans, Eduard Soudijn en Jan Vos. Hij is getrouwd met Geertruid van Wassenaer; zij hebben drie dochters, Clara, Diede en Ottolien.

Colofon

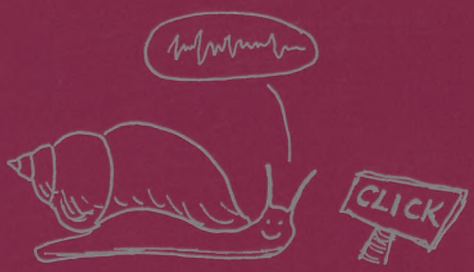
Lay-out advies: M.W. Helsper-Peters

Omslagontwerp: CT Graphics

Drukwerk: Benda BV, Nijmegen

Publication of this thesis was generously supported by:

Abbott, ALK Benelux, ARTU Biologicals, ASTA Medica (Allergodil), ASTRA Pharmaceutica (Rhinocort), Cara C'air, GN Danavox, Electro Medical Instruments, Entermed, Glaxo Wellcome, HAL Allergenen, Hoechst Marion Roussel (Sofradex, Rulide), Janssen-Cilag, Mediprof, Moduvice Medical Products, Ooms Allergie, Oticon, Pfizer Bartlett (Zithromax), Philips Hoortoestellen, ReSound, Roche Nederland, Schering-Plough, Smith&Nephew, SmithKline Beecham, Stöpler, UCB Pharma, Veenhuis Medical Audio, Yamanouchi Pharma



ISBN 90-9009282-X