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On Pressure Regulation of the Middle Ear

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2010

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Life is like a box of chocolate, you never know what you are going to get

Forrest Gump

PAPERS

This thesis is based on the following studies, which will be referred to in the text by their Roman numerals. The studies are appended at the end of the thesis.

I *Chronic Tympanic Membrane Perforation: Middle Ear Pressure and Tubal Function*
M Brattmo, B Tideholm, B Carlborg
Acta Otolaryngol 2003; 123: 569-574

II *Middle Ear Pressure Equilibration Ability and Spontaneous Pressure Changes in Healthy Ears with Ventilation Tubes*
M Brattmo, B Tideholm, B Carlborg
Acta Otolaryngol 2005; 125: 702-706

III *Attic Cholesteatoma –Long-term Measurement of the Middle Ear Pressure*
M Brattmo, B Tideholm, B Carlborg
Manuscript

IV *Disturbed Opening Capacity of the Eustachian Tube in Meniere's Disease*
M Brattmo, B Tideholm, B Carlborg
Submitted

ABBREVIATIONS

ABG	Air bone gap
AC	Attic cholesteatoma
ADC	Analogue to digital converter
CCP	Chronic central perforation
ET	Eustachian tube
MD	Meniere's disease
ME	Middle ear
pCO_2	Partial pressure of carbon dioxide
pO_2	Partial pressure of oxygen
PTA	Pure tone average
SD	Standard deviation
TM	Tympanic membrane
VT	Ventilation tube

UNITS OF PRESSURE

1.00 kPa	=	100 daPa	=	102 mm H_2O	=	7.50 mm Hg
1.00 mm Hg	=	0.133 kPa	=	13.3 daPa	=	13.6 mm H_2O
100 mm H_2O	=	98.1 daPa	=	0.981 kPa	=	7.36 mm Hg

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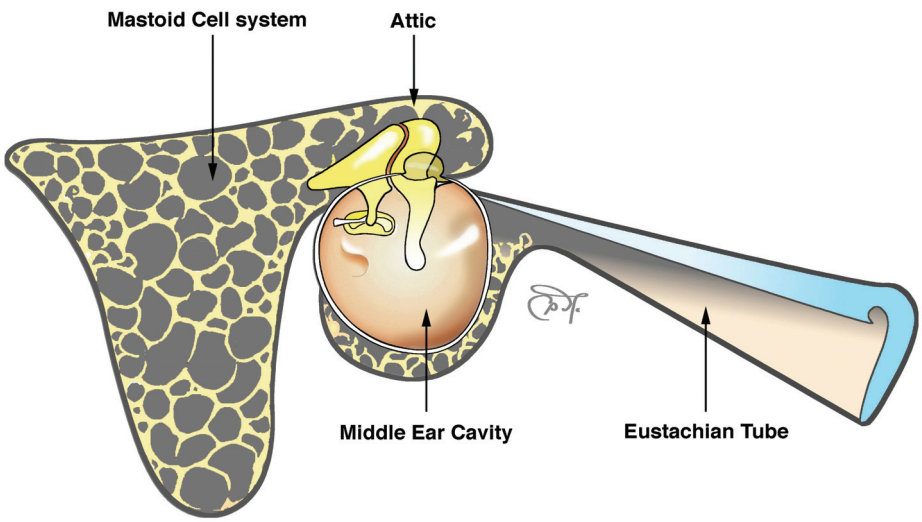
1. INTRODUCTION

1.1 Background

The ear and the auditory system are essential for communication and awareness of danger. The function of the middle ear (ME) is to transmit sound waves in the air to the fluid in the inner ear as efficiently as possible. Movement of the tympanic membrane (TM), in response to pressure changes in the external ear, results in vibration of the ossicular chain. These vibrations are transferred to the scala tympani of the inner ear, passing through the oval window. In addition, the ME serves as a transformer, increasing the sound transmission to the inner ear. The transducer function of the ME is most advantageous when the TM is in the neutral position, i.e. when the ambient and the ME pressures are in equilibrium. A pressure gradient over the TM will increase the acoustic impedance and reduce the efficiency of sound transmission. ME pressure homeostasis is important in maintaining a healthy ear and failure in the regulation of this pressure, may lead to pathological consequences. Negative ME pressure and impaired function of the Eustachian tube (ET) are associated with the development of chronic ME diseases, such as cholesteatoma, chronic tympanic membrane retraction, secretory otitis media and chronic central perforation (Ingelstedt 1964, Magnuson 1981, Falk 1982, Bylander 1986, Wolfman & Chole



1986, Mink & Bauer 1993).

The *hydrops ex vacuo* theory was accepted for many years as the principle of pressure regulation in the ME (Politzer 1867). In this theory it was postulated that the gas in the ME was continuously absorbed by the mucosa and that a negative ME pressure was established if there was no equilibrations via the ET. Prolonged negative pressure was believed to result in the release of a transudate into the ME, to compensate for the negative pressure, thus reducing the volume of the cavity. Several studies, concluding that the obstruction of the ET was the origin of negative ME pressure, have been presented (Ingelstedt & Jonson 1966, Sade 1966, Bluestone 1971, Buckingham & Ferrer 1973). The *hydrops ex vacuo* theory was first questioned when an increase, instead of a decrease, in the ME pressure was reported in situations where tubal openings are relatively few, such as bed rest and just after waking (Bylander, Tjernstrom et al. 1985, Hergils & Magnuson 1987). Furthermore, no decrease in ME pressure was observed in an experimental study of dogs in which the ET had been blocked (Buckingham, Stuart et al. 1985).

Nowadays, the most commonly accepted theory of ME pressure regulation in healthy ears, is bi-directional gas diffusion over the ME mucosa, aided by intermittent pressure equilibration via the ET (Hergils & Magnuson 1988, Sade & Luntz 1991, Ars & Ars-Piret 1994). The relative contributions to the total ME pressure of the gases oxygen, carbon dioxide and nitrogen have been thoroughly studied (Felding, Rasmussen et al. 1987, Grontved, Moller et al. 1990, Hergils & Magnuson 1990, Ostfeld & Silberberg 1991, Sade & Luntz 1991). In healthy ears with an intact TM, the composition of the gas in the ME and the venous blood are similar, indicating an effective diffusion. The gases oxygen and carbon dioxide move most easily through the mucosa and are therefore assumed to contribute most to the pressure change in the ME, resulting from variations in the partial pressures in the venous blood (Fink, Ar et al. 2003). The ME pressure has been observed to increase during sleep in healthy ears. This was assumed to be the effect of a reduction in pulmonary ventilation during sleep, with a subsequent rise in carbon dioxide in the venous blood and diffusion into the ME (Douglas, White et al. 1982, Hergils & Magnuson 1987, Shinkawa,

Okitsu et al. 1987, Schafer 1998, Tideholm, Carlborg et al. 1998, Tideholm, Brattmo et al. 1999). Nitrogen is believed to influence the fluctuations in ME pressure to a lesser degree, due to its relatively constant partial pressure in the venous blood and its lower diffusion rate (Fink, Ar et al. 2003).

The ET has at least three functions in ME homeostasis: ventilation of the ME to equilibrate the pressure with the atmospheric pressure; drainage and clearance of secretions produced in the ME into the nasopharynx; and protection of the ME from nasopharyngeal sound and secretions. The ET is normally collapsed due to the elastic properties of the cartilage and surrounding tissues. Voluntary and involuntary actions such as swallowing, yawning, sneezing and shouting can cause temporary opening. Spontaneous opening, due to pressure gradients between the ME and nasopharynx, have been observed in laboratory tests (Magnuson 1981, Tideholm, Carlborg et al. 1998, Bunne, Falk et al. 2000). The opening and closing properties of the ET show great variations, in subjects with healthy ears and those with diseased ears, and in test-retest measurements on the same subject (Elner, Ingelstedt et al. 1971, Falk & Magnuson 1984, Tideholm, Carlborg et al. 1998, Bunne, Falk et al. 2000).

The mastoid cell system is regarded as a functional part of the ME but its physiological role has not been fully elucidated. The septa of the mastoid bone cells are covered by a thin layer of respiratory epithelium, creating a large surface area. The cell system has been suggested to be a passive container, an extra volume serving to shield the ME from rapid pressure changes (Diamant 1958, Sade 1992). It has also been suggested that it protects the inner ear, especially the vestibular part, from temperature changes (Magnuson 2003). The pneumatized area and volume of the system have been calculated, in healthy and diseased ears, using temporal bone imaging. The average area in healthy ears has been found to be 12 cm^2 (using conventional tomography); and the volume 7.9 and 7.1 cm^3 (using CT-scans) (Diamant 1958, Koc, Ekinci et al. 2003, Lee, Jun et al. 2005). The mastoid cell system in patients with chronically diseased ears is generally smaller or is not pneumatized than in subjects with healthy ears. An inverse relation has been reported between the pneumatization of the mastoid

cells and the severity of the disease, i.e. ears with a deep pars flaccida retraction pocket in the TM had a small or non-pneumatized mastoid cavity (Sade, Fuchs et al. 1996).

1.2 Chronic central perforation

Chronic central perforation (CCP) of the TM can be a consequence of trauma or infection or a sequela to treatment in the form of a myringotomy or the insertion of a ventilation tube (VT). The normal healing of a perforation might be delayed by persistent infection, but little is known about the healing process of an acute perforation (Gladstone, Jackler et al. 1995, Stenfeldt, Johansson et al. 2006). In clinical practice it is accepted that a persistent perforation could compensate for poor ET function, particularly in children and adolescents (Gladstone, Jackler et al. 1995). Children with healthy ears and children with secretory otitis media both showed a poorer capacity to equalize induced pressures than adults (Bylander, Ivarsson et al. 1981, Falk 1982). Children show a greater unpredictability in this capacity, both in test-retest situations and inter-individually (Falk & Magnuson 1984, Bunne, Falk et al. 2000). Based on these findings, the authors concluded that a single ET function test was of little prognostic value for the individual.

Adults with CCP have demonstrated a poor capacity to equilibrate induced positive and negative pressures in ET function tests (Andreasson & Ivarsson 1976, Mink & Bauer 1993). It is possible that the delayed healing of a CCP is influenced by this, and that these ears have impaired ME pressure regulation. The ME pressure in ears with CCP is equal to the atmospheric pressure. If these ears are sealed off from ambient pressure, as in the case in the pressure-measuring method used in this work, the ME pressure can be monitored. It has been reported that the gas composition in MEs open to the atmosphere, as in cases of CCP or VT, is similar to that in air, i.e. about a 15% higher oxygen concentration than in the venous blood (Felding, Rasmussen et al. 1987). It was assumed that this influenced the measurement of ME pressure due to the diffusion of oxygen from the ME. The higher oxygen concentration in the open ME might impair the opening capacity of the ET (Shupak, Tabari et al. 1996). Inserting a VT in healthy ears one week prior to the pressure measurements, will lead to a gas composition and pressure in the ME, similar to those in ears with a CCP

(Grontved, Moller et al. 1990, Fink, Ar et al. 2003). The conditions in ears with CCPs and healthy ears with VTs, will then be as similar as possible at the beginning of the measurements, and any difference in the ME pressure regulation can be detected.

1.3 Attic cholesteatoma

The TM can be separated into 2 distinct parts, the pars tensa, and the upper and smaller pars flaccida. The latter has a surface area approximately 1/25-50 of the former. The pars flaccida has a connective tissue layer with a thicker and a less dense structure than the pars tensa (Lim 1995, Stenfeldt, Johansson et al. 2006). The function of the pars flaccida is not fully understood but it has been suggested that it has a pressure equilibrating function, thus protecting the pars tensa from retracting (Shrapnell 1832, Sade 1997). This theory has been questioned due to the small area and volume displacement of the pars flaccida (Dirckx, Decraemer et al. 1998). Another theory that has been put forward is that it acts as a pressure detector, and is involved in the reflex initiating the opening of the ET (Hellstrom & Stenfors 1983). A negative ME pressure can cause either total or partial retraction of the TM. Atrophic scars on the pars tensa and the less dense connective tissue structure in the pars flaccida predisposes to localized retractions (Magnuson, Hellstrom et al. 1995). In addition, the embryologic mucosal folds, dividing the ME and the attic into separate compartments are considered to be important for the development of localized retractions (Proctor 1964, Miyanaga & Morimitsu 1997, Palva, Ramsay et al. 1998). Cholesteatomas are particularly prone to develop in these retracted areas (Sade 1980).

Up until the late 1970s most authors were convinced that a negative ME pressure was caused by a longstanding obstruction of the ET (Ingelstedt 1964, Buckingham & Ferrer 1973). Studies on behavioural sniffing and closing failure of the ET have shown that the aetiology of the retraction is more complex, and that extreme negative pressure can be generated by active evacuation of ME gases through the ET, i.e. sniffing (Magnuson 1978, Magnuson 1981). Using questionnaires and laboratory tests, it has been estimated that sniffing behaviour occurs in 24-27% of patients with unilateral cholestea-

toma and in 70-84% of patients with bilateral cholesteatomas (Kobayashi, Yaginuma et al. 1996, Tsuji, Sone et al. 2002, Ohta, Sakagami et al. 2009). Attic cholesteatoma (AC) develops in a retraction pocket of the pars flaccida. Pure AC, in which the pars tensa is not affected, is a rare disease constituting approximately 6% of all cholesteatomas (Felek, Islam et al. 2009). It is unclear as to what extent a negative ME pressure influences the development of AC, or if the retraction is attributable to the quality of the pars flaccida with its relative weakness compared with the pars tensa.

1.4 Meniere's disease

In 1861, Prosper Meniere described the symptoms of intermittent attacks of vertigo, hearing loss of increasing severity and noises in the ear (Meniere 1861). The underlying patho-physiological cause of Meniere's disease (MD) is endolymphatic hydrops, which can only be demonstrated with certainty by a histopathological study of the temporal bone after death (Hallpike & Cairns 1938; AAO-Guidelines 1995). For clinical purposes, MD is term used to refer to the syndrome triad of: recurrent, spontaneous episodic vertigo; cochlear hearing loss; and tinnitus and/or aural fullness (Gibson 1983, AAO-Guidelines 1995). Research on MD is mostly focused on the inner ear and the ME has been regarded as the main path for treatment of the inner ear when using various pharmacological, mechanical and surgical methods (Merchant, Rauch et al. 1995).

Malfunction of the ET and the impairment of ME pressure regulation have been suggested to be causal in the development of MD. In 1966, Tumarkin presented his theory on the combination of blockage of the ET, negative ME pressure and inadequacy of the cochlear aqueduct, as the cause of development to endolymphatic hydrops (Tumarkin 1966). Relief of symptoms in acute attacks was reported when subjects with MD were exposed to underpressure in a pressure chamber, and consequently a positive ME pressure (Ingelstedt, Ivarsson et al. 1976). Several studies using tympanometry have confirmed ET blockage and negative ME pressure in MD (Hall & Brackmann 1977, Morinaka & Nakamura 2004), while others have reported the opposite (Cinnamond 1975, Forquer & Brackmann 1980; Maier, Ross et al. 1997). Insertion of a VT through the TM can prevent severe fluctuations in ME pres-

sure, and clinical reports have shown improvement in vertigo symptoms after insertion of a VT (Montandon, Guillemin et al. 1988; Sugawara, Kitamura et al. 2003; Park, Chen et al. 2009). However, no improvement was seen in vestibular function (Park, Chen et al. 2009). Transtympanic micropressure therapy (Meniett®) is an alternative treatment modality in MD (Thomsen, Sass et al. 2005). A VT is inserted prior to therapy in order to allow the pressure pulses to be transmitted to the inner ear. No improvement in symptoms has been reported during the time between VT insertion and the start of therapy (2 weeks) (Odkvist, Arlinger et al. 2000; Gates, Green et al. 2004).

The influence of pressure changes in the ME on the inner ear fluid has been demonstrated in experimental studies in animals. Rapid pressure changes in the ME cavity were transmitted to the inner ear fluid. The effect was governed by a complex interaction between the rate of pressure change, the patency of the cochlear aqueduct and the characteristics of the endolymphatic sac (Carlborg, Densert et al. 1982; Konradsson, Carlborg et al. 1997; Feijen, Segenhout et al. 2000).
MD originates from the inner ear with the development of endolymphatic hydrops and to date there are no convincing studies demonstrating the contribution of the ME pressure. Despite this, improvements in vertigo symptoms have been reported after the insertion of a VT through the TM. This might indicate disturbance in the function of the ET and ME pressure regulation.

1.5 Methods of middle ear pressure measurement

Two essentially different kinds of methods can be used to measure the functioning of the ET and ME pressure. Direct methods require contact with the ME space, indirect methods leave the tympanic cavity intact and the results are recorded across the TM. The latter can be used for momentary measurement, or series of momentary measurements, but are not suitable for continuous measurements.

Auscultation from the ear canal was one of the first indirect methods described. An increasing pressure was applied to the nasopharynx by a catheter. The opening of the ET could be heard as a “click” via the external auditory canal by the examiner (Toynbee 1853). Otomicroscopic observations have been used to determine TM movement and

retraction after insufflation of gases or ET provocation tests (Zollner 1963, Luntz & Sade 1990, Sade & Luntz 1991). In the pneumophone method, TM impedance characteristics have been utilized (Van Dishoeck 1941). Using the same principle the tympanometry method for measuring ME pressure was developed (Metz 1946, Thomsen 1955, Liden, Peterson et al. 1969, Jerger, Jerger et al. 1972). A constant sound is presented in the external ear canal and a sweeping pressure change is induced, from positive to negative. The sound reflected from the TM is registered by a microphone. When the pressure in the ME and external canal are equal the reflected sound has minimal intensity. The tympanometry method is now widely used in both research and clinical practice. To evaluate the patency of the ET, a pressure chamber to manipulate the ME pressure, has been used in combination with tympanometry (Bylander, Ivarsson et al. 1981). Another technique used to evaluate the patency of the ET is the microflow method (Ingelstedt & Ortegren 1963; Elner, Ingelstedt et al. 1971). A flow meter placed in the external ear canal measures the displacement of the TM when the ME pressure is changed by varying the pressure in a pressure chamber and the subject performing ET function tests. Sonotubometry is a method used for measuring the ET opening pressure by sound conduction during swallowing (Virtanen 1978, Holmquist, Bjorkman et al. 1981, Mondain, Vidal et al. 1997).

Several authors have described direct methods of measuring ME pressure and ET function in human, by TM perforation, i.e. inflation-deflation and forced-response techniques (Flisberg 1966; Buckingham & Ferrer 1973, Andreasson & Ivarsson 1976, Cantekin, Saez et al. 1979, Mink, Bauer 1993). A method has been developed for the bilateral measurement of ME and nasopharyngeal pressure, allowing the pressures to be compared simultaneously in the 3 compartments, as response to various tests, e.g. the sniff test. (Magnuson 1981; Bunne, Falk et al. 2000) Access to the ME via puncture of the mastoid cell system (Ingelstedt, Ivarsson et al. 1967, Kawabata, Nomura et al. 1985, Hergils, Magnuson et al. 1990, Alper, Banks et al. 2003) and through the ET has been described (Takahashi, Hayashi et al. 1987, Kaneko, Doi et al. 1996).

The methods described above have been used to measure the ME pressure momentarily and in laboratory settings. A method of direct, continuous, long-term and ambulant measurement has been developed by our group (Tideholm, Jonsson et al. 1996). The subjects can be monitored in their normal daily environments for up to 24 hours. Rapid pressure events and longstanding pressure changes can be identified in the measurements. The monitoring was combined with provocation tests of ET patency. This method makes it possible to analyse the ME pressure over time and relate it to the ET function. This method was used in the studies presented in this thesis and is described more detail in Chapter 3.

2. AIMS

The studies upon which this thesis is based were designed to achieve the following aims:

- To elucidate the mechanism of ME pressure regulation, by monitoring the ME pressure with the method for direct, continuous, long-term and ambulant measurements of ME pressure and by studying the ET function by provocation tests of the ET patency.
- To investigate whether long-term ME pressure measurements and ET provocation tests, give separate and characteristic information on the pressure regulation and its effect on the ME pressure over time.
- To investigate whether combined analysis of the results from the dual mode of the method gives additional information useful for the understanding of ME pressure regulation compared to results from only one method.
- To evaluate whether subjects with CCP, whose MEs are sealed off from the ambient air, have impaired ME pressure regulation compared with subjects who have healthy ears.
- To describe the ME pressure regulation in healthy ears with VTs in comparison with healthy ears without VTs and ears with CCP.
- To further develop the monitoring method to improve its capability to analyse rapid pressure changes and to allow longer measuring times in investigations of subjects with AC and MD.
- To investigate the ME pressure in ears with AC with regards to: the magnitude of the negative ME pressure; sniff-induced, repeated, rapid negative pressure changes; and the patency of the ET.
- To elucidate whether the functioning of the ET and ME pressure regulation in ears with MD are impaired.

3. METHODS AND SUBJECTS

3.1 Equipment

A piezo-electric pressure transducer (SenSym®) was connected via an instrument amplifier and a low-pass filter to an 8-bit analogue to digital converter (ADC) mounted in a computer. The electronic components were housed in a plastic box, measuring 120 x 60 x 35 mm. The 8-bit ADC gave a resolution of 3.9 daPa. The measurement range of the pressure transducer was ±500 daPa. In the ET function tests the sampling rate was 18.2 Hz, giving a sampling interval of 0.06 s (Tideholm, Jonsson et al. 1996). The ambulant, long-term measurements required portable equipment which was worn in a chest harness. From the low-pass filter, the signal was connected directly to an 8-bit ADC, a crystal-driven clock, a logical unit and a digital memory, mounted in a box, measuring 130 x 70 x 35 mm. The sampling rate was 1.25 Hz and the resolution 3.9 daPa. A special program was used for data analysis. The power was supplied by two 9 V alkaline batteries (Tideholm, Jonsson et al. 1996). This system was used in Studies I and II.

The above system was further developed to improve the pressure resolution, sampling rate and battery life and to achieve more friendly equipment thus permitting even longer recording times. The processor consisted of a 16-bites microcomputer (Texas instruments, MSP 430®) with an ADC and a differential pressure sensor (Silicon Microstructures, SM800®). The measurement range was ±500 daPa and the resolution was 0.24 daPa. The components were mounted in a box, measuring 100 x 50 x 20 mm, with an LCD (DPL500). Data were sampled and analysed using the software DPL500 Graph USB. Data obtained in long-term measurements were stored on a secure digital memory card at a sampling rate of 10 Hz. The sampling rate in the ET function tests was 100 Hz. The system was battery-driven using rechargeable Li-On batteries with a maximum capacity of 48 hours. The equipment was worn in a custom made vest and was used in Studies II and III.

3.1.1 Auxiliary equipment

The equipment was connected to the ME by a polyethylene tube with a

diameter of 0.76 mm and a length of 35 cm. The tube penetrated a hearing protector (Comfit® ear plug), which was inserted tight and deep into the external ear canal. The dead space was estimated to be approximately 0.6 ml. During the ET-function tests an air-filled syringe with a valve was attached to the system. This allowed for equilibration and adjustment of the ME pressure according to the requirements of the test situation. It also enabled tests to make for leakage in the measuring system (Tideholm, Jonsson et al. 1996).
The different systems used in the Studies I-II and III-IV have been tested and found to meet the requirements for correct pressure recordings within the measurement range, temperature stability and baseline stability (Tideholm, Jonsson et al. 1996).

3.2 Investigation procedures

Access for direct pressure measurement in the ME was obtained by a perforation of the TM. The air tightness of the ear plug and measuring system was checked by manually increasing the ME pressure to +100 daPa. A stable pressure level for 5 minutes indicated that there was no leakage. In Study I, all the subjects had a CCP. In study II-IV myringotomy was made on all subjects, using topical anaesthesia (Phenol®). In Studies II and IV the perforation was kept open by inserting a VT. All subjects in each study were subjected to two separate pressure investigations: ET function/provocation tests and continuous, long-term and ambulant measurements.

3.2.1 ET provocation tests

Before conducting the long-term pressure measurements, the following ET provocations tests were performed:

1. Valsalva's manoeuvre: defined as effective when 3 of 3 trials yielded a positive pressure and at least one reached ≥500 daPa.
2. Toynbee's manoeuvre: defined as positive if the ME pressure was changed by at least 10 daPa following at least 1/3 deglutitions with the nose occluded.
3. Opening pressure of the ET. The ME was exposed to continuously increasing pressure, towards a maximum of +500 daPa during a period of 10 s. The opening pressure was defined as the level at which a sudden drop in pressure, ≥50 daPa, occurred.
4. Sniff test: defined as positive if at least 1/3 powerful nasal inha-

lations resulted in a fall in ME pressure of at least 50 daPa.

5. Pressure equilibration ability: classified into four tubal function groups (Elner, Ingelstedt et al. 1971). The subjects of Group I could completely equilibrate ±200 daPa induced in the ME by 3 deglutitions or less. In Group II equilibration of positive and negative pressures was incomplete, resulting in a residual pressure of less than 20 daPa. The subjects in Group III could equilibrate positive but not negative pressures and those in Group IV could not equilibrate induced pressures at all.

3.2.2 Continuous long-term measurements

The ET provocation tests were followed by continuous long-term measurements of the ME pressure. This was performed on ambulant subjects, during the day and night for 16-19 hours in their normal environments. The recordings started in the late afternoon, and lasted for at least 4 hours before going to bed, during sleep and at least 2 hours after getting up in the morning. The subjects were encouraged to perform normal everyday activities. They were also instructed to fill in a time sheet noting certain activities, such as going to bed and the estimated time of falling asleep and waking up in the morning.

3.2.3 Follow-up

Otomicroscopy was performed on all subjects after each measurement had been concluded, after 1 week, or upon request by the subjects. All perforations caused by myringotomy had healed within 1 week. All perforations after extraction of the VTs had healed within 2 months.

3.2.4 CT-scan in Study IV

CT scans of the temporal bone were performed on 9/11 subjects with AC. The mastoid pneumatization volume was calculated using software from Siemens AG (Somatom Sensation 16®). The objective of the scan was also to confirm tissue obliteration of the attic with bony erosions indicative of cholesteatoma. An aerated ME cavity supports the clinical diagnosis of AC and confirms the possibility of performing valid ME pressure measurements.

3.3 Subjects

3.3.1 Study I

Thirty consecutively identified adult patients with CCP fulfilled the criteria and were included in the study. They were identified 3-6 months prior to myringoplasty at the Department of Otorhinolaryngology, University Hospital, Malmö. The perforations had lasted for at least 6 months, with no ear infection during the past 3 months. Subjects with other known ear pathology were not included in the study. Seven of thirty subjects had to be excluded from the study due to incomplete recordings caused by pressure leakage (5), discomfort in the ear canal causing termination of the measurement (1) and technical problems (1). Twenty-three subjects thus completed the entire investigation, 12 of which were female (52%). The mean age was 41 years (range 18-68). The mean hearing level according to pure tone average (PTA) was 38 dB HL (range 2-88) and the mean air bone gap (ABG) was 20 dB (range 0-36).

3.3.2 Study II

Twenty-four adult subjects with healthy ears volunteered for the investigation. The inclusion criteria were no history of ear disease, infection or allergy giving rise to symptoms in the upper airways. The subjects had normal hearing and normal findings at otomicroscopy. Six out of the twenty-four subjects were excluded due to incomplete recordings caused by pressure leakage (1) and technical problems (5). Eighteen subjects thus completed the entire investigation, 11 of which were female (61%). The mean age was 30 years (range 18-48). The measurements were performed 1 week after the insertion of VTs.

3.3.3 Study III

Thirteen consecutive adult patients with unilateral AC were included in the study. They were identified at the Department of Otorhinolaryngology, University Hospital, Malmö and met the following inclusion criteria: aerated ME cleft, no sign of retraction, perforation, or infection of the pars tensa of the TM; otomicroscopic findings of a deep retraction of the pars flaccida with squameous epithelium debris retained deep into the attic and visible bony erosion. The diagnosis was supported by CT scan and confirmed by surgery approximately 1 week

after the measurements. Exclusion criteria were: previous ME surgery in the affected ear, infection or allergy giving rise to symptoms in the upper airways. Two of the thirteen subjects were excluded from the study due to discomfort in the ear canal caused by the ear plug, leading to interruption of the measurement. Eleven subjects thus completed the entire investigation. Their mean age was 40 years (range 26-57) and 5 were female (45%). Hearing tests using PTA revealed a mean HL of 32 dB and a mean ABG of 17 dB. The perforations were patched as part of the surgical treatment for cholesteatoma.
The ME pressure data were analysed to identify tubal opening and sniffing. Tubal opening was defined as a sudden pressure change towards zero. The pressure change was required to reach a maximum velocity of at least 100 daPa/s. Tubal openings could be incomplete, i.e. not reaching atmospheric pressure. A sniff was defined as a rapid (within 1 s) fall in pressure greater than 50 daPa. The maximum velocity of the pressure fall was required to reach 100 daPa/s.

3.3.4 Study IV

Twenty-seven consecutive patients with unilateral MD, identified at the Department of Otorhinolaryngology, University Hospital, Malmö, were included in the study. The diagnosis met the requirements for definite MD, as given in the AAO Guidelines (AAO-Guidelines 1995). An additional inclusion criterion was: ≥2 attacks of vertigo, each lasting 20 minutes to 4 hours, during the past 3 months. Cochlear hearing loss was confirmed by repeated PTA and brainstem audiometry. The exclusion criteria were: previous surgery for ME or treatment with VT in the affected ear, infection or allergy giving rise to symptoms in the upper airways. Six of twenty-seven subjects had to be excluded due to incomplete recordings caused by leakage in the measuring system (3) and other technical problems (3). Thus, 21 subjects completed the entire investigation, 16 of which were female (76%). The mean age was 55 years (range 28-85), and the mean duration of the disease was 6.0 years (range 3 months to 20 years). The measurements were preceded by the insertion of VTs.

3.3.5 Controls – Studies for comparison

Two separate studies had been performed previously in subjects with healthy ears, using the method described above. The previous studies

included 20 subjects, 10 subjects in each study (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). The subjects had no ongoing or previous history of ear disease during their adult years. They showed normal tympanometry and otomicroscopy findings. Their mean age was 31.5 years (range 22-47). All had a hearing level better than 20 dB HL. The investigation protocols for ET provocation tests and ambulant long term measurements were similar to those in the studies described here.

3.4 Statistics

Raw data from the continuous ME pressure measurements were transferred to the SPSS program. SPSS was used to obtain average values, and to reduce the great amount of data. The mean values were used to create graphs and illustrations created in Microsoft Excel. The number of subjects in the groups was relatively few and non-parametric tests (the Wilcoxon signed rank test and the Mann-Whitney test) were therefore appropriate in most cases. The variance is expressed as the standard deviation (SD) over time periods, calculated with SPSS.

SPSS software program was also used for the statistical analysis of the provocation test results. The T-test, the Wilcoxon's signed rank test, the Mann-Whitney test and the chi-squared test were used for the calculations and group comparisons of the data. A value of $p<0.05$ was considered statistically significant.

3.5 Ethics

The investigations were approved by the Research Committee on Ethics, Lund University, Sweden (LU 185-93 and LU 21-2005).

4. RESULTS

4.1 Study I

Results of the ET provocation tests revealed that 4/23 subjects were unable to perform Valsalva's manoeuvre and none showed a positive sniff test results (Table 2). In 8/23 subjects the ET was not forced opened by a ME pressure of 500 daPa (Table 3). Twenty of the twenty-three subjects showed a reduced ability to equilibrate induced pressures by deglutition, Groups III-IV (Table 4).

The continuous long-term ME pressure measurements in the subjects with CCP were divided into 4 periods. 1. the coupling period; defined as the first 2 hours of measurement, 2. the period of erect body position, 3. the sleeping period and 4. the period after getting up in the morning. The coupling period was characterised by an immediate fall in pressure in 19/23 subjects, giving a mean ME pressure after 2 hours of –60.0 daPa, and a mean ME pressure during the first 3 hours of measurement of –46.0 daPa (Fig. 1). A mean negative ME pressure was observed during the period of erect body position, but the pressure level showed considerable individual variations. The ME pressure increased in all subjects just before and during the first hour of sleep.

Table 1. Mean ME pressure (daPa) and standard deviation (SD) in several different 1 hour observation periods during the long-term measurements in 21 subjects with CCP. Healthy ears refer to a compilation of results from 2 previous studies (Tideholm, Carlborg et al. 1998, Tideholm, Brattmo et al. 1999).

Period	CCP; mean (daPa) ±SD	Healthy ears; mean (daPa) ±SD
Third hour after start	–64 ±68	–9 ±11
Last hour before sleep	–41 ±70	–13 ±29
Second hour asleep	+3 ±46	+20 ±20
First hour awake in the morning	–23 ±41	

Table 2. Results of the ET provocation tests in studies I-IV: Valsalva's- and Toynbee's manoeuvers and sniff test. Healthy ears refers to the results from 2 previous studies (Tideholm, Carlborg et al. 1998, Tideholm, Brattmo et al. 1999).

	Study I CCP n=23	Study II Healthy ears VTs n=18	Study III AC n=11	Study IV MD n=21	Healthy ears n=20
Valsalva's manoevre	83%	100%	55% (6)	57%	100%
Toynbee's manoevre	26%	28%	36% (4)	38%	40%
Sniff test	0%	17%	18% (2)	0%	10%

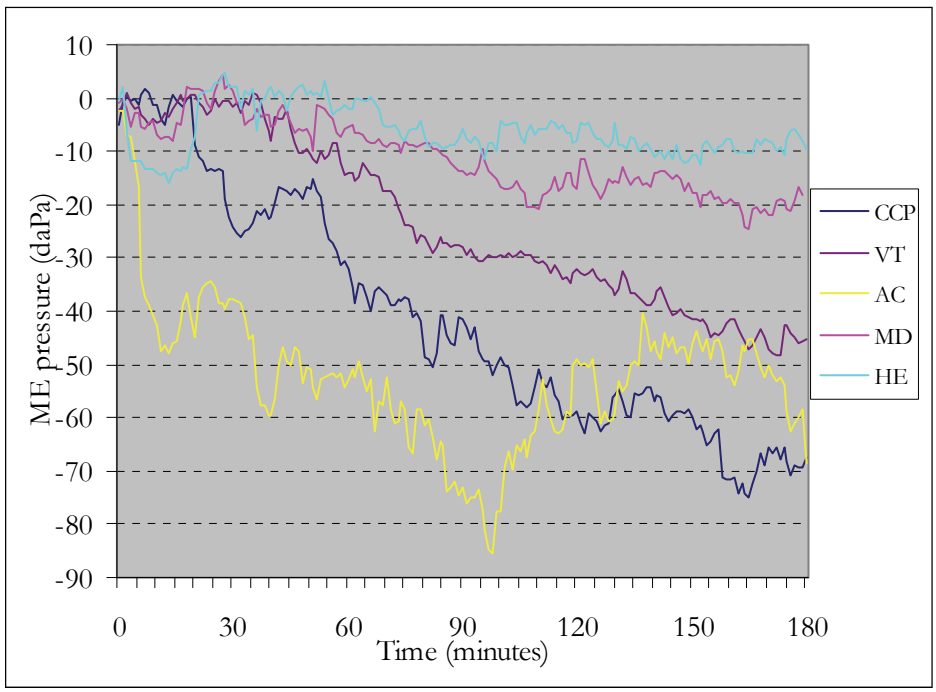


Fig 1. The mean ME pressures during the 3 first hours of continuous measurements in 23 subjects with CCP, 18 subjects with healthy ears and VTs (VT), 11 subjects with AC and 21 subjects with MD. The combined results of 2 studies in 20 subjects with healthy ears (HE) are shown for comparison (Tideholm, Carlborg et al. 1998, Tideholm, Brattmo et al. 1999).

The higher pressure was maintained during the period of sleeping. The mean ME pressure in the 2 hours prior to falling asleep and the first 2 hours asleep was –56.0 and –1.0 daPa, respectively ($p<0.001$) (Fig. 2). During the period after getting up in the morning the ME pressure declined again. The mean ME pressure during the last 2 hours of sleep and the first 2 hours after getting up was +11.1 and –26.2 daPa, respectively ($p=0.006$) (Fig. 3).

The mean number of tubal openings was 0.9/hour during the first 5 hours of measurements. A tubal opening, resulting in an immediate increase in pressure towards zero, was shortly followed by a negative pressure trend. The long-term measurements demonstrated that the ME pressure varies over time in individuals and between individuals. This was illustrated by the large SD when comparing the mean ME pressure

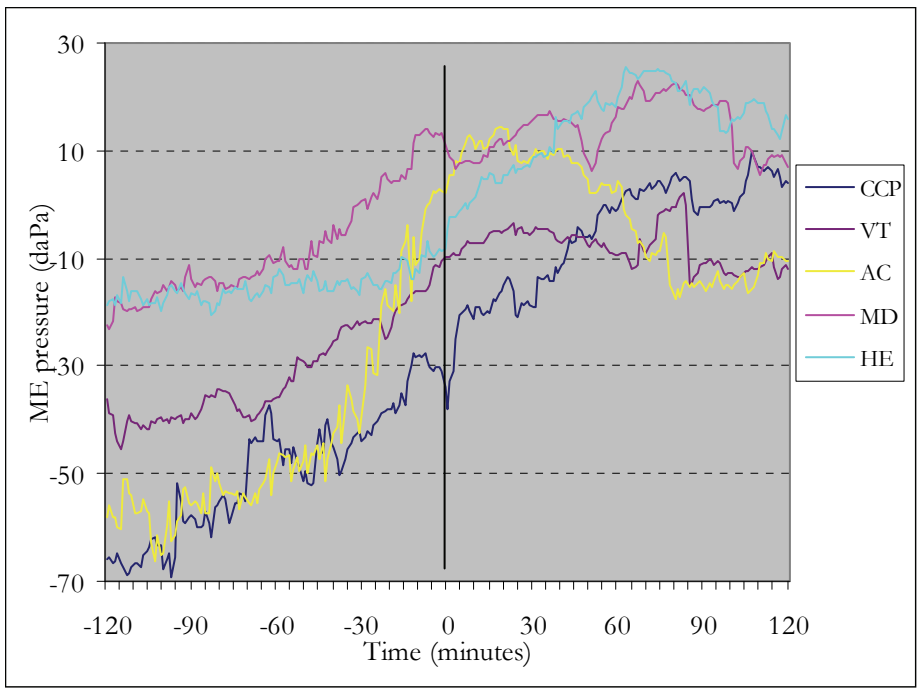


Fig 2. The mean ME pressure during the last 2 hours before sleep and the first 2 hours of sleep in 23 subjects with CCP, 18 subjects with healthy ears and VTs (VT), 11 subjects with AC and 21 subjects with MD. The combined results of 2 previous studies in 20 subjects with healthy ears are shown for comparison (Tideholm, Carlborg et al. 1998, Tideholm, Brattmo et al. 1999). Time 0 indicates the time of falling asleep.

during the different observation periods in subjects with CCP and those with healthy ears (Table 1).

4.2 Study II

The continuous long-term measurements revealed a negative trend in 10/18 subjects with healthy ears and VTs. The ME pressure during the first 3 hours of measurement was –27 daPa (Fig. 1). The ME pressure rose when the subjects went to bed and fell asleep. The mean ME pressure during the last 2 hours before falling asleep and the first 2 hours of sleep was –36 and –9 daPa, respectively (p=0.002) (Fig. 2). The pressure remained at this higher level during sleep and declined again when the subjects got up in the morning. The mean ME pressure during the last 2 hours of sleep and the first 2 hours after getting up was –1 and –17 daPa, respectively (p=0.005) (Fig. 3).
The 18 subjects were divided into 2 subgroups (A and B) according to the results of the continuous measurement. Subgroup A (10/18) demonstrated an initial slow decrease in ME pressure, giving a mean pressure of –49 daPa during the first 3 hours of measurement. In the ET function tests they exhibit a reduced ability to equalize induced ME pressures. They were distributed to tubal function Groups III and IV. Subgroup B (8/18) had a mean ME pressure around zero during daytime. Six belonged to tubal function Group I and 2 to Group III.

Table 3. Opening pressures of the ET in studies I-IV. Healthy ears refer to the compilation of the results from 2 previous studies (Tideholm, Carlborg et al. 1998, Tideholm, Brattmo et al. 1999).

	Study I CCP n=23	Study II Healthy ears - VTs n=18	Study III AC n=11	Study IV MD n=21	Healthy ears n=20
Opening pressure level <50 daPa	9%	22%	9% (1)	5%	5%
Opening pressure level ≥50 to ≤500 daPa	57%	61%	64% (7)	62%	95%
Opening pressure level >500 daPa	35%	17%	27% (3)	33%	0%

4.3 Study III

The provocation tests of ET patency revealed that 5/11 subjects with AC could not perform Valsalva's manoeuvre effectively, and 9/11 subjects could not change their ME pressure by performing powerful sniffs (Table 2). Their ability to equalize induced pressures of ±200 daPa was clearly reduced (Table 4).

The mean ME pressure of all 11 subjects was –52.7 daPa during the first 3 hours of measurement (Fig. 1). One subject had a ME pressure around the atmospheric pressure during the daytime. Four had continuously negative pressure during the first 3 hours of measurement, mean –77.0 daPa. Six subjects had episodes of repeated, rapid, negative pressure changes, fulfilling the criteria for sniffing episodes. These epi-

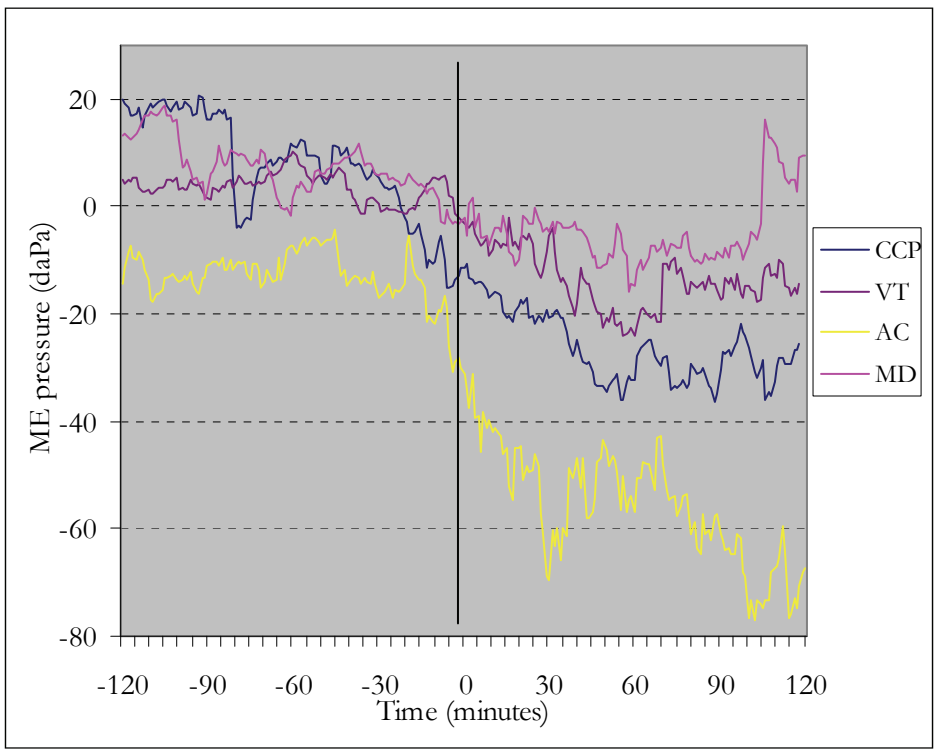


Fig 3. The mean ME pressure during the last 2 hours of sleep and the first 2 hours awake in the morning in 23 subjects with CCP, 18 subjects with healthy ears and VTs (VT), 11 subjects with AC and 21 subjects with MD. Time 0 indicates the time of getting up.

sodes occurred only during the daytime and each episode lasted from 30 minutes to several hours. Each separate sniff resulted in a negative pressure change of 50-220 daPa (Fig. 4). CT-scans of the temporal bones was performed in 9/11 subjects. Three revealed an entirely sclerotic mastoid, 4/9 subjects had small pneumatised volumes (range 0.5-2.1 cm^3) and 2/9 had a fully pneumatised mastoid bone (volumes 5.0 and 7.2 cm^3).

4.4 Study IV

In the ET provocation tests 9/21 subjects with MD were unable to perform Valsalva's manoeuvre effectively (Table 2). In 7/21 subjects a pressure exceeding 500 daPa in the ME was needed to force the ET open (Table 3). Attempts to equalize ME pressures of ±200 daPa resulted in full equilibration ability in 6/21 subjects, 3/21 subjects could equilibrate only positive pressure, and 12/21 subjects could not equilibrate induced pressures at all (Table 4).

The long-term ME pressure measurements revealed a slight negative pressure during the daytime. The mean pressure during the first 3 hours of measurement was –11.0 daPa. When the subjects went to bed and during the period of sleep the common pattern of ME pressure rise was seen. The mean pressures during the last 2 hours before sleep and

Table 4. Distribution of the subjects between different tubal function groups (Group I-IV), according to their ability to equalize pressures induced in the ME (Elner, Ingelstedt et al. 1971). Healthy ears refers to the compilation of the results from 2 previous studies (Tideholm, Carlborg et al. 1998, Tideholm, Brattmo et al. 1999).

	Study I CCP n=23	Study II Healthy ears-VTs n=18	Study III AC n=11	Study IV MD n=21	Healthy ears n=20
Group I	13%	39%	9% (1)	29%	85%
Group II	0	0	0	0	15%
Group III	22%	28%	27% (3)	14%	0
Group IV	65%	33%	64% (7)	57%	0

during the first 2 hours of sleep were –7.7 daPa and +14.1 daPa, respectively (p=0.037) (Fig. 2). The magnitude of the pressure changes showed individual variations, as well as variations between patients.

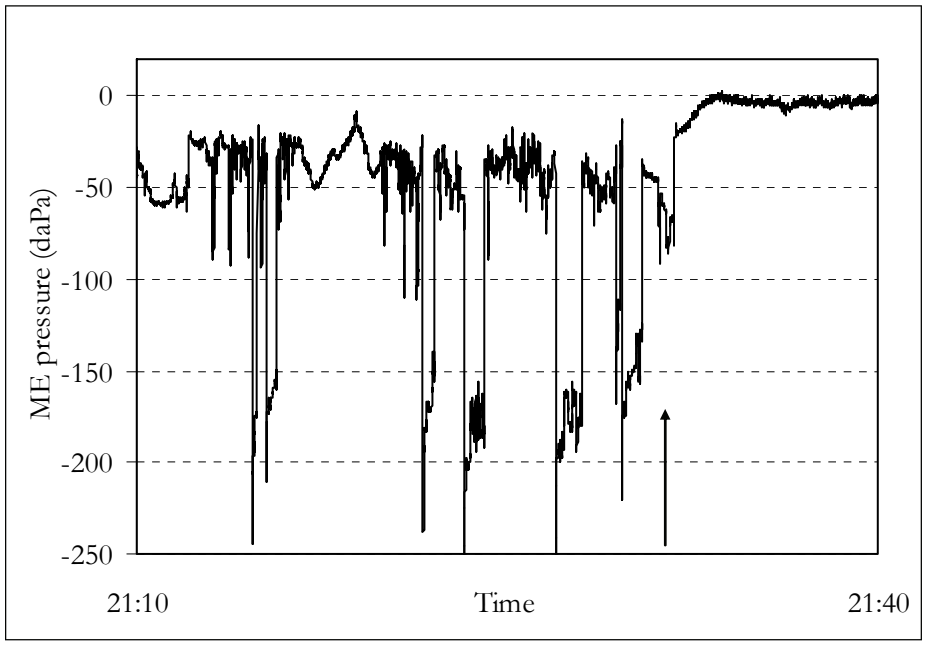


Fig 4. Graph showing sniff induced repeated rapid negative pressure changes and tubal openings in one subject with AC over a period of 30 minutes. The subject's estimated time of falling asleep was 21.30 (arrow). The subject had no sniffning episodes during sleep.

5. DISCUSSION

5.1 General discussion

The four studies described in this thesis were designed to reveal patho-physiological ME pressure conditions in chronic ear diseases. This was accomplished by continuously monitoring the ME pressure, to record its variability during normal daytime and night-time activities and by combining the results with findings of ET provocation tests. The results obtained from the four investigations were compared with each other and with the results from two previous studies on healthy ears (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). The study was not designed to elucidate the cause of the diseases nor the effects of treatments.

As the results of the four investigations in this study were compared with those obtained in healthy ears in earlier studies, there was a risk of selection bias, although this was judged to be small as the subjects were selected from different populations. In order to minimise the risk of observer's bias we used only 2 investigators.

5.1.1 Methodological considerations

The method of continuous, direct, long-term measurement of the ME pressure in combination with provocation tests of ET patency was developed by our research group (Tideholm, Jonsson et al. 1996). It was used in all the investigations described in this thesis and has a number of advantages compared with previously used methods:

- Because it is a direct technique, it reveals rapid pressure changes, such as those following ET equilibration or a sniff. Measurements with an indirect technique, such as tympanometry and the microflow method, is preceded by a provocation of the ME and measures movements of the TM, and such rapid pressure changes cannot be detected (Metz 1946; Ingelstedt & Ortegren 1963).
- The sampling rate in the continuous measurement was high and sufficient: 1.25 and 10 Hz, for analysis of rapid, relevant pressure changes. A high sampling rate is not possible to obtain with indirect techniques.
- The portable equipment makes it possible to monitor the varia-

tion in ME pressure during normal everyday activities and sleep.

- This direct method measures the ME pressure via a TM perforation, and can be used to study chronic ear diseases, whereas indirect methods are influenced by the quality and movement of the TM.

However, the method has also some disadvantages which must be taken into account when analysing the results:

- As the TM of healthy ears is intact, the measurements must be preceded by a myringotomy. This poses ethical restrictions, on the number and size of control groups, as there can be a delay of TM healing.
- The volume of the tubing and connectors must be added to the ME volume. To minimise this volume bias the ear plug was inserted as deeply as possible into the external ear canal, approximately 5-10 mm laterally to the TM. The polyethylene tube connecting the measuring device to the ear plug was thin (inner diameter 0.76 mm) and short (35 cm). The calculated extra volume added to the system was 0.6 ml. This increase in the total volume might influence the absolute peak pressure values recorded during the fast pressure changes, but did not influence the possibility of detecting them (Tideholm, Jonsson et al. 1996).
- The ear plug had to be inserted into the external ear canal so as to avoid the leakage of gas. Each measurement was preceded by a thorough test to ensure that there was no leakage. Six subjects had to be excluded from the four studies due to leakage.
- The long-term measurements (16-19 hours) caused discomfort in some of the subjects due to the ear plug. Three subjects in the four studies terminated the measurements because of pain in the external ear canal.

5.2 Provocation tests of ET patency

In this work five different tests were used to evaluate the ET patency. They were designed as provocation tests and were not primarily expected to reveal information on the contribution of ET functioning to ME pressure regulation during the normal, unprovoked conditions experienced in daily life. Three of the tests have been originally described and used for healthy ears using the microflow technique in a pressure chamber (Elner, Ingelstedt et al. 1971). These tests were

adapted to suit the direct measuring method used here. The three tests were complemented with the sniff test and the test to determine the opening pressure and were chosen to monitor different aspects of the ET function (Tideholm, Jonsson et al. 1996).

The results of the ET provocation tests differed in all four of the present studies compared with these obtained from healthy ears in earlier studies (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). The difference was most pronounced in the ability of the subjects to equilibrate induced pressures of ±200 daPa by deglutition (Table 4). This was especially prominent in subjects with MD, AC and CCP. The ability to equalize this level of negative pressure is an important function of the ET and relevant in daily life. The long-term continuous measurements showed that a prevailing pressure level around –200 daPa was not uncommon. The ability to effectively perform Valsalva's manoeuvre was reduced in the subjects with AC and MD (Table 2). The results of Toynbee's manoeuvre and the powerful sniff test did not show any differences between any of the four studies, or between these studies and the previous studies on healthy ears.

5.3 Continuous ME pressure measurements

The subjects with CCP, healthy ears with VTs and those with AC demonstrated a distinct fall in mean pressure during the first hours of the continuous long-term measurements (Fig. 1). Due to the perforation of the TM, the MEs of subjects with CCP and healthy ears with VTs have had, prolonged communication with the atmosphere and consequently the properties of the gas mixture in the MEs will be similar to those of air (Felding, Rasmussen et al. 1987). Ears with intact TMs have been found to have a mixture of gases more like that dissolved in the venous blood, and the partial pressure of oxygen (pO_2) has been found to be about 15% lower than that in air (Felding, Rasmussen et al. 1987; Hergils & Magnuson 1990; Ostfeld & Silberberg 1991). When the ears with CCP and the healthy ears with VTs were sealed off from the environment at the beginning of the continuous pressure measurements, diffusion started to balance out this difference, resulting in a fall in ME pressure. This process is considered to reach a steady state within 2 hours (Yee, Cantekin 1987; Doyle, Seroky 1994). The mean ME pressure fall levelled off after a couple of hours, but the negative ME pres-

sure remained for the rest of the day and evening. An inadequate equilibration capacity was revealed in the subjects with CCP by fewer tubal openings than in healthy ears, and this presumably increased the negative pressure (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). Also, each tubal opening resulting in a pressure rise towards zero, was shortly followed by a negative pressure trend. This indicated gas diffusion from the ME possibly associated with the pathologic condition in ears with CCP however, the same procedure was used in the two previous studies in healthy ears, and the results would thus have been influenced in the same way.

The results from all four studies showed increasing ME pressure around the estimated time of falling asleep and stabilization of the pressure during sleep at a higher level than during the day (Fig 2). This appears to be a general trait of ME pressure regulation, since it was also observed in the two previous studies on healthy ears (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). During sleep the rate of pulmonary ventilation falls, resulting in an elevation of the partial pressure of carbon dioxide (pCO_2) in the venous blood (Douglas, White et al. 1982; Schafer 1998). The increase in pressure was therefore, probably due to the diffusion of carbon dioxide into the ME. In the morning hours the reverse was seen, i.e. a decline in ME pressure (Fig. 3). This can be explained by the increased pulmonary ventilation after getting up in the morning and the diffusion of carbon dioxide from the ME. However, this effect does not seem to account completely for the decline in mean ME pressure seen in the subjects with CCP and AC.
It is suggested that gas diffusion from the ME and insufficient ET equilibrations, characteristic of these pathological ear conditions, contributed to the negative pressure recorded in these ears during the morning hours. Six of eleven subjects with AC had episodes of sniff-induced rapid, negative pressure changes during the morning hours, and this presumably contributed to the considerable mean ME pressure in the subjects with AC. The ME pressure pattern of subjects with MD did not differ from in the long-term measurement from that in the previously studied healthy ears (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). It is interesting to note that two such different diseases like MD and AC showed similar pathological results in

the ET provocation tests, while showing strikingly different results in the long-term continuous measurements. This is an indication of the complexity of the mechanisms governing ME pressure regulation, and demonstrates the importance of monitoring several indicators.
The long-term continuous measurements revealed large intra- and inter-individual pressure variations, reflected in SD (Table 1). This is a consequence of the ability of the method to reveal the dynamics of pressure regulation, i.e. responses to daily activities, tubal opening and sniffing. The statistical analysis was therefore applied to mean values obtained over periods of 2-3 hours of measurements.

5.4 Special observations in Studies I-IV

Earlier studies on subjects with CCP have reported a reduction in the function of the ET, like in our study (Andreasson & Ivarsson 1976; Virtanen, Palva et al. 1980; Mink & 1993). An improvement in ET function following tympanoplasty has been demonstrated and the use of preoperative ET function tests has been discussed (Ekvall 1969; Andreasson & Harris 1979; Reimer, Andreasson et al. 1988; Mink & Bauer 1993). The reduced ability to equilibrate ME pressure in ET tests was reflected in the long-term measurements reported here, showing few occasions of tubal openings. This contributed to a considerable mean negative ME pressure during the daytime in subjects with CCP.

Inserting VTs into the TM of subjects with healthy ears one week prior to the measurements, ensured that gas mixture in the ME was the same as in the ambient air, as is the case in the subjects with CCP, with about a 15% higher pO_2 (Felding, Rasmussen et al. 1987; Doyle & Seroky 1994). The results of the investigation of healthy ears with VTs differed from those obtained from healthy ears without VTs, regarding both the equalization tests and the continuous measurements (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). This indicates that prolonged exposure of the ME to the atmospheric air influences the ME pressure regulation. Consequently, the results in these two studies support the theory that the opening, *per see,* impaired or contributed to the impairment in the regulation of ME pressure.

Pressure regulation by sniff-induced negative ME pressure changes was a characteristic finding in the long-term measurements in the sub-

jects with AC. Interestingly, in the ET provocation tests only 2/11 subjects were able to produce a positive sniff test result on demand. In the long-term measurements, 6/11 subjects demonstrated episodes of repeated, sniff-induced negative changes, a behaviour that the subjects seemed to be unaware of (Fig. 4). The prevalence of sniffing has been estimated to be 24-27% patients with unilateral cholesteatomas in earlier investigations based on questionnaires and laboratory tests (Kobayashi, Yaginuma et al. 1996; Tsuji, Sone et al. 2002; Ohta, Sakagami et al. 2009). The present results indicate an even higher incidence in the subjects with unilateral AC, and that sniff tests in a laboratory setting and questionnaires do not reveal all subjects with this habit. It can therefore be concluded that the continuous measurements during normal daily activities is the method of choice for detect subjects with a sniffing habit.

The episodes of repeated, rapid pressure changes in the continuous measurements showed great inter- and intra-individual difference in all the 6 subjects with a sniffing habit. Variations were seen in the magnitude of the negative peaks, the number of sniffs per unit time, the length of each episode, as well as the numbers of episodes. The subjects with a sniffing habit showed a reduced opening capacity in the ET equalization tests. In spite of this, they had large number of tubal openings during the episodes of sniffing, indicating tubal closing failure (Fig. 4). More sniffing episodes were observed in the morning hours than the evening hours and, no episode was seen during sleep. Only 2/23 subjects with CCP, none with MD and none with healthy ears, with or without VTs, had sniffing episodes. In spite of the reduced opening capacity seen in the ET function tests and the negative ME pressure recordings in the long-term measurements, there were no signs of pars tensa retraction of the TM in the subjects with AC.

The investigation of subjects with MD revealed a high resistance to ET opening in the provocation tests, i.e. a reduced ability to equilibrate induced positive and negative ME pressures, and to perform Valsalva's manoeuvre effectively. The results of the long-term measurements did not differ from those found earlier in healthy ears (Tideholm, Carlborg et al. 1998; Tideholm, Brattmo et al. 1999). The results reported in Studies I-III indicated a correlation between reduced equilibration ca-

pacity in ET provocation tests and a negative mean ME pressure during the daytime. This correlation was not seen in the study on subjects with MD and emphasizes the advantage with the dual mode procedure used in this work. The reduced capacity of the ET to equilibrate induced pressures in the provocation tests indicates that subjects with MD are more likely to be exposed to prolonged significant ME pressures in daily life. The implications of this are speculative. Experimental studies in animals have demonstrated that pressure changes in the MEs are transferred to the inner ear fluid (Carlborg, Densert et al. 1982; Feijen, Segenhout et al. 2002). When the cochlear aqueduct was blocked, the negative ME pressure transmitted to the inner ear was found to be prolonged, thereby increasing the inner ear volume (Konradsson, Carlborg et al. 1997). This provides some support for the theory that a combination of a blocked ET, negative ME pressure and inadequacy of the cochlear aqueduct, is a cause of development of endolymphatic hydrops (Tumarkin 1966).

During the past 10 years, the treatment of MD with VTs has become frequent at some medical centres. This is surprising in light of the unproven effect of this treatment, except for a few clinical reports indicating reduction of vertigo attacks (Montandon, Guillemin et al. 1988; Sugawara, Kitamura et al. 2003; Park, Chen et al. 2009). The subjects with MD in the present study demonstrated a reduction in the opening capacity of the ET. The clinical relevance of this finding can only be speculative upon, and was not the purpose of this investigation. Treatment with VTs protects the ME from longstanding significant pressures changes, thus providing some theoretical support for the use of VTs in patients with MD.

6. CONCLUSIONS

The conclusions of this study can be summarised as follows.

- Investigations using the method of direct, continuous, long-term and ambulant measurements of ME pressure and ET provocation tests were performed successfully in subjects with CCP, AC, MD and in those with healthy ears with VTs.
- A characteristic seen in subjects with pathological ME conditions was a negative ME pressure during the daytime. This reflects the diffusion of gas from the ME, in combination with few and insufficient ET equalizations. This findings was interpreted as impaired ME pressure regulation and was seen in the majority of subjects with CCP, AC and healthy ears with VTs.
- In all four studies some subjects showed daytime ME pressure varying around zero, as was also seen in the vast majority of subjects in two earlier studies on healthy ears.
- The two different types of measurements complemented each other, e.g. the long-term continuous measurements revealed the specific ME pressure changes caused by sniffing in the majority of the subjects with AC. The sniff provocation test alone was inadequate in detecting these subjects.
- The results of all four studies revealed an increase in mean ME pressure and stabilization at a higher pressure level during sleep than in the daytime. This pressure increase is believed to be caused by the diffusion of carbon dioxide into the ME.
- Subjects with CCP showed the characteristic of negative ME pressure during the daytime both before and after sleep. They also had a poor ability to equalize induced pressures in ET provocation tests.
- A negative ME pressure was observed in healthy ears with VTs in the daytime. This is in contrast to the results of the previous studies on healthy ears without VTs. The MEs of the subjects with healthy ears and VTs and those with CCP had been opened to the ambient air, and the results of these two studies gave sup-

port to the theory that the opening, per see, impaired the ME pressure regulation.

- The subjects with AC showed a continuous daytime negative ME pressure and/or sniff-induced, rapid, negative ME pressure changes, in spite of a normal pars tensa and a mainly aerated ME. These findings indicate a clear relation between the occurrence of AC and impaired ME pressure regulation.
- The episodes of sniff-induced rapid, negative ME pressure changes, in the subjects with AC, were associated with a greater number of tubal openings demonstrating tubal closing failure. Despite this, the majority of subjects with AC were found to have a reduced tubal opening capacity, revealed in their inability to equalize induced pressures by deglutition and Valsalva's manoeuvre.
- The subjects with MD had a reduced ability to perform Valsalva's manoeuvre and a reduced capacity to equilibrate induced pressures. This indicates that subjects with MD are more likely to be exposed to prolonged ME pressures changes in daily life.
- The modified equipment, used in Studies III and IV, with improved time resolution, made it possible to analyse sniff-induced negative ME pressure changes in detail.
- The results of the studies in this thesis have contributed to improving our understanding of the regulation of ME pressure in ears with pathological conditions. However, other studies are required to further elucidate the causes of chronic ear diseases. The possibility of complementing clinical investigations with this direct continuous long-term measurement of ME pressure should be investigated.

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8. SAMMANFATTNING PÅ SVENSKA

Mellanörats funktion är att överföra och förstärka ljudvågor från luften till innerörats vätska. Denna överföring är optimal när trumhinnan är i neutral position, dvs när trycket i mellanörat och omgivningen är lika. Avvikelser i mellanörats tryck ses vid kroniska mellanöresjukdomar, fr a är det visat ett samband mellan negativt tryck och sjukdomstillstånd som sekretorisk otit (vätska i mellanörat), retraktioner (indragningar av trumhinnan) och cholesteatom (benröta i örat).
Mellanörats tryck regleras av gasdiffusion över mellanöreslemhinnan i kombination med intermittenta öppningar av örontrumpeten. Gasdiffusionen styrs av de tryckgradienter som uppstår när gaskoncentrationerna i mellanörats hålrum och blodet skiljer sig åt. De gaser som är kända för att påverka det totala trycket är koldioxid, syrgas och kvävgas. Diffusionhastigheten mellan dessa skiljer sig åt, då koldioxid har förmågan att uppnå jämvikt inom några minuter, syrgas inom några timmar och kvävgas troligen inte på flera dygn. Örontrumpeten är i det friska örat stängd men öppnar sig bl a i samband med sväljningar och gäspningar.

Forskningsintresse för mellanörats tryckreglering i friska såväl som sjuka öron har funnits i många år. De metoder som har använts har kunnat mäta mellanöretrycket och örontrumpetens öppningsförmåga endast med momentana registreringar i laboratoriemiljö. Vår forskargrupp har utvecklat en metod för kontinuerlig mätning av mellanöretrycket i kombination med provokationstester av örontrumpeten. Med metoden mäts mellanöretrycket direkt via ett litet hål i trumhinnan. Ett hörselgångsskydd placeras med total täthet i hörselgången. Detta förbinds med mätutrustningen, som bärs i en sele på bröstet. Mätningarna börjar med provokationstesterna och därefter startas den kontinuerliga mätningen, som pågår i 16-19 timmar i daglig normal aktivitet och sömn i hemmiljö. Personer med friska öron har tidigare undersökts med vår metod. De visade ett likartat mönster med ett medeltryck under dagtid strax under atmosfärstrycket och med ökning till positivet under sömn. Denna tryckökning beror på att lungventilationen sjunker i sömn, med ökad koldioxidhalt i blodet, vilket medför en nettodiffusion av koldioxid in till mellanörat.
De fyra studier som ingår i denna avhandling är gjorda med syfte att

öka förståelsen för de fysiologiska mekanismer som styr tryckregleringen i sjuka öron. Undersökningarna gjordes på patienter med kroniska trumhinneperforationer, atticus cholesteatom och Meniere's sjukdom samt på personer med friska öron som fått insatt ventilationsrör genom trumhinnan.

Mellanöron med kr perforationer är öppna mot omgivningen och har ett mellanöretryck som motsvarar atmosfärstrycket. Våra mätningar gjordes för att bedöma förmågan till tryckreglering. När mätningarna började och mellanöronen stängdes av mot omgivningen av hörselproppen uppstod ett uttalat negativt medeltryck, som kvarstod under tiden patienterna var vakna. Resultaten visade också en nedsatt förmåga till att utjämna pålagt positivt och negativt tryck med sväljningar i provokationstesterna. Det negativa trycket kunde delvis förklaras av att en gasdiffusion med syrgas från mellanörat började när mätningarna inleddes. Syrgashalten i det öppna mellanörat är ca 15% högre än i ett mellanöra med intakt trumhinna.
För att klargöra påverkan av den högre syrgashalten på våra resultat gjordes en undersökning på friska öron med ventilationsrör, vilka applicerades 1 vecka före undersökningen. Gaskoncentrationerna i mellanöronen kunde då förutsättas ha anpassat sig till luftens, med 15% högre syrgashalt. Resultaten visade att 10/18 fick ett uttalat negativt tryck och 8/18 hade ett tryck som var lätt negativt eller runt 0 under dagtid. De personer som hade ett uttalat negativt tryck hade alla utom en nedsatt förmåga att svälja undan pålagt tryck, fr a negativt, vid provokationstester. Slutsatsen blev att öppningen av trumhinnan i sig, kan ge försämring av tryckregleringen i mellanöron.

Patienter med atticus cholesteatom har benröta som utgår från en indragningsficka i trumhinnans översta del. Resten av mellanörat och trumhinnan är opåverkade och det har diskuterats om mellanörats tryck och tryckreglering kan vara en orsak i utvecklingen av denna sjukdom. Undersökningarna visade ett uttalat negativt medeltryck och reducerad förmåga till tryckutjämningar i provokationstester. Tryckmönstret varierar mellan patienterna. 1/11 hade ett tryck som fluktuerade runt 0, 4/11 hade ett jämnt negativt tryck utan snabba fluktuationer, 6/11 hade perioder med snifforsakade upprepade snabba negativa tryckfall. Majoriteten av patienterna hade sniffbeteende, men endast 2/11 kunde i

provokationtesterna skapa tryckfall vid sniff test. Slutsats blev att det avvikande trycket och den störda tryckregleringen med sannolikhet var förenade med utveckling av atticus cholesteatomen, samt att den kontinuerliga mellanöretryckmätningen var överlägsen provokationstester för att avslöja sniffbeteende.

Patienter med Meniere's sjukdom lider av återkommande anfall av yrsel, hörselnedsättning och tinnitus. Sjukdomen har sitt ursprung i innerörat men undersökningar har visat att avvikelser i mellanörats tryck möjligen kan påverka symtomen, troligen via trycköverföring till innerörat. Resultaten visade att 15/21 patienter inte kunde utjämna pålagt positivt och negativt tryck med sväljningar och att 9/21 inte kunde skapa tryckökning med Valsalva's manöver. Alla personer i de tidigare mätningarna på friska öron kunde utföra dessa tester effektivt. Trots detta visade de kontinuerliga mätningarna ett likartat mönster i de två grupperna. Slutsats blev att det är troligt att patienter med Meniere's sjukdom i sin dagliga miljö, när de utsätts för tryckökningar och tryckfall i mellanöronen, inte har förmåga att tryckutjämna via örontrumpeten på ett adekvat sätt och att detta möjligen kan ge tryckpåverkan på inner örats vätskor.

Slutsatsen är att metoden för kontinuerlig, direkt mellanöretryckmätning är väl användbar för att fysiologiskt beskriva mellanörons tryck och örontrumpetens funktion i sjuka öron. Undersökningarna har gett en ökad förståelse för tryckregleringen i sjuka öron. Framtida studier behövs för att ytterliggare klarlägga mellanöronens tryckreglering och sambandet med orsaker/utveckling av öronsjukdomar.

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