Chapter 5
Quasi-static Pressures in the Middle Ear Cleft

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Keywords Baroreceptors • Cholesteatoma • Eustachian tube • Gas exchange • Obliteration • Otitis • Pars flaccida • Perforation • Retraction pockets • Ventilation tubes

5.1 Introduction

The primary function of the middle ear (ME) is to allow efficient transfer of sound waves from the air-filled external ear canal to the inner ear cochlear fluid. The closed ME cavity prevents acoustic shortcut over the tympanic membrane and thus contributes to sound sensitivity, especially at low frequencies. The volume of the cavity needs to be large enough so that the eardrum can vibrate freely. Modern ME research has been aimed predominantly at investigating its acoustic function. The ME is also a semirigid biological gas pocket that is closed most of the time and therefore is subject to slower quasi-static variations between the pressure in the external ear canal and the ME cavity. These quasi-static pressure changes can be several orders of magnitude larger than the loudest tolerable dynamic sound pressures. Many researchers agree that there is a close relationship between ME

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pressure (de)regulation and pathology of the tympanic membrane (TM) as well as the ME, but many questions still remain regarding the underlying mechanisms.

This chapter deals with several aspects of quasi-static pressures in the ME. It explains how ME pressure can be measured, discusses the different factors involved in regulating ME pressure, and comments on the connections between ME pressure deregulation and ME pathology. Lastly, some recent results are discussed that explore the role of neural mechanisms in regulating quasi-static pressures in the ME.

5.1.1 Units and Definitions

In young normal hearing humans, hearing sensitivity is limited to frequencies ranging between approximately 20 Hz and 20 kHz. Apart from audible sound, which is a periodically alternating pressure signal, a "DC" pressure component may also be present. Such static pressure differences between the outside world and the ME cavity never stays exactly constant. Hence, because the pressure continuously changes, "static pressure" in the ME does not exist in practice. ME pressure is therefore "quasi-static," albeit over a broad and varying range of time scales. In the literature, the terms static and quasi-static pressures are used interchangeably to describe these slower pressure changes. Whether such pressure changes are referred to as very low frequency sound or as slow pressure variation is rather arbitrary. In this chapter, the term "quasi-static" pressures is used, meaning pressure variations on time scales that are slower than the lowest frequency of audible sounds, say 20 Hz.

In acoustics, sound pressure level, or pressure amplitude, is given in decibels sound pressure level (dB SPL) relative to a reference sound pressure level of 20 μPa (in air). The threshold of hearing at 1,000 Hz is on the order of 0 dB SPL for a normal hearing young adult, while the loudest tolerable sound pressure is on the order of 120 dB SPL. The thresholds of both hearing and pain strongly depend on the frequency. For quasi-static pressure variations it is less customary to use the dB SPL scale; the amplitude of the pressure level is instead usually given on a linear scale. In the past, several different units have been used to indicate the amplitude of pressure in the ME. Traditionally, in tympanometry, many authors used "millimeters of water pressure" (mm H_2O), where 1 mm of water column corresponds to approximately 9.8 Pa (slightly depending on temperature). As clinicians grew accustomed to reading tympanograms on the "millimeter water scale," the change to SI units was made by using "decaPascals" (daPa), which was very close to the previously used unit. In the scientific literature, pressures are expressed in Newtons per square meter, or the appropriate SI unit: Pascal (Pa).

5.1.2 The Presence of ME Pressures

Quasi-static pressure variations, which lead to pressure differences between the ME cavity and the surrounding environment, are an essential part of everyday life. During the course of a day, gradual meteorological changes in ambient pressures can easily be on the order of several kiloPasacals. Under artificial circumstances, such as taking a fast elevator, airplane travel, or in a ski descent, ambient pressure can also change by several kiloPascals over a period of a few seconds. In suddenly submerging the head in water, a dive of just 1 m deep causes a pressure increase of 10 kPa in a fraction of a second.

The preceding examples are extrinsic sources of pressure difference between the ME cavity and the outside world. Physiologic processes within the ME itself can also cause a buildup of pressure differences. First, the exchange of gases between the ME cleft (the combined structure of ME cavity and mastoid) and the gases dissolved in the blood perfusing the mucosa can gradually deplete the gas content of the ME cleft (Loring and Butler 1987). Second, changes in mucosa volume can alter the ME cleft volume and consequently alter the pressure (Magnuson 2003).

From the preceding examples it is clear that the ME has to constantly deal with pressure changes on the order of tens to thousands of Pascals. The pressure changes can occur on very different time scales, from fractions of seconds to hours. These pressure changes, which occur under normal circumstances of everyday life, are far larger than the highest pressure amplitudes of the acoustic pressure range. At 120 dB SPL, the pressure amplitude is just a mere 10 Pa, whereas submerging the head 10 cm into a bathtub already causes a pressure load of 1 kPa.

5.1.3 Mechanisms of ME Pressure Changes

Figure 5.1a is an artist's impression of some of the mechanisms involved in ME pressure regulation. This section provides a short overview of the most important processes involved in ME pressure regulation.

The ME cavity is connected to a porous part of the temporal bone called the mastoid that consists of many air-filled cells. The connected volume of the ME cavity and the mastoid is referred to as the ME cleft. Both the interior wall of the ME and the air cells are covered with mucosa that is perfused by blood vessels. The Eustachian tube (ET) forms a connection between the ME cavity and the nasopharynx, and under normal circumstances it is closed. The TM forms a nonrigid wall of the cavity. Gases can leave or enter the cavity either through the ET or by gas exchange with the blood through the mucosa. The volume of the ME cleft can change due to deformations of the TM as well as to changes of the mucosa thickness. The process of gas exchange may be part of a centrally controlled feedback mechanism, with the TM as a possible pressure detector. Figure 5.1b

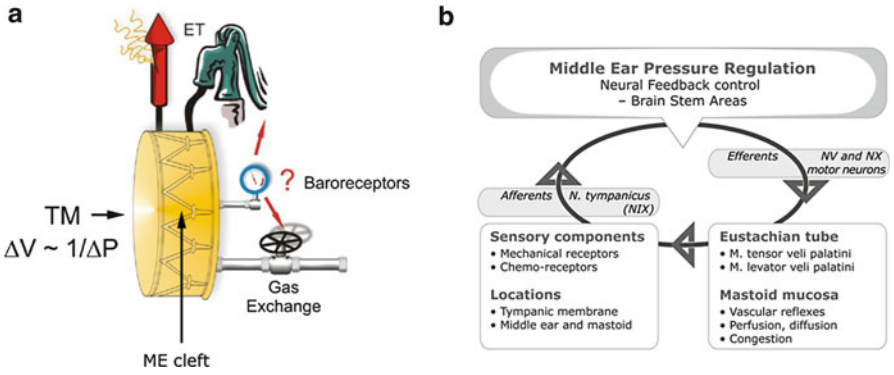

Fig. 5.1 (**a**) An artist's impression of the pressure regulation mechanisms in the middle ear (*ME*). The ME ear cavity together with the mastoid (a porous part of the skull bone) is called the ME cleft. This cleft forms a gas-filled volume (represented by the *yellow drum*). The drum has a fixed volume content, except that the drum membrane, the tympanic membrane (*TM*), can be displaced. For a fixed amount of gas, the product of volume and pressure is constant, so volume change ΔV by deformation of the TM leads to pressure change ΔP. The Eustachian tube (*ET*) opens at high pressure differences between the ME and ambient pressure, acting as a vent or safety valve. It may also act as a pump, injecting small boluses of air into the ME. Gas exchange between the ME cleft and the blood can change ME pressure significantly over long time scales. Indications exist that baroreceptors are present in the ME, which may be involved in an active feedback mechanism controlling ET opening and gas exchange. (**b**) Diagram illustrating the factors involved in neural feedback mechanism for the overall control of ME pressure. Afferent stimuli containing information about the ME pressure project to brain stem areas (nucleus of the solitary tract) that communicate with the nucleus ambiguus and the trigeminal motor nucleus. Efferents projects via NV and NX motor neurons to the tensor veli palatini and levator veli palatini muscles. In addition, mastoid perfusion may be influenced by vascular reflexes by afferents of the n. tympanicus deriving from the motor nucleus of the dorsal respiratory group (*NX*)

gives an overview of the neural components involved in the process. The details are explained in Sect. 5.8.

If the ME was an all-rigid and closed cavity, any pressure change in the outside world would result in a pressure difference between the cavity and the outside of exactly the same magnitude. Because the TM exhibits viscoelastic properties, it can deform when it is loaded with pressure. Part of this load is compensated by a volume change in the ME cavity. Simultaneously, strain is developed in the TM and in ME structures. The TM consists of two major parts: the pars tensa, which is connected to the manubrium, and the much more elastic pars flaccid, which is situated superiorly to the malleus. The size of the pars flaccida differs strongly between different species; in some, it is nearly absent, whereas in others it is even as large as the pars tensa (Decraemer and Funnell 2008). The pars flaccida can deform very easily, but in most species, including humans, it is far smaller than the pars tensa. Owing to its conical and curved shape, the pars tensa may also easily bend. These membrane deformations will change the volume enclosed in the ME cavity. At larger pressure differences, strain and stress in the pars flaccida and the pars tensa increase, and beyond $\pm$ 2 kPa the TM becomes increasingly stiff. At these pressures the role of

the TM as a regulator disappears, and the membrane becomes a victim of the pressure load, which may have clinical consequences, as discussed later.

In addition to its role in the clearance of ME fluid, the ET plays an important role in pressure regulation. Although nowadays it is known that the ET is not an open tube at all, but rather a tissue fold that opens only momentarily, its name suggests the old concept of a constant vent. Under normal circumstances it is closed and during swallowing the tube opens actively, allowing small amounts of air into the ME. For larger positive pressure differences between the ME and the nasopharynx, the ET opens passively, allowing gas under overpressure to leave the ME. In this way one may divide the ET action in two functions. On the one hand it operates as a slow regulator of minor pressure differences by gradual (quantized) admittance of small amounts of gas into the ME, while on the other hand it acts as an emergency valve protecting the ear from excessive pressure loads. Direct measurements of ME pressure have shown both slow continuous changes of pressure and more sudden stepwise changes related to ET openings. In general, large pressure differences will result in ET openings and pressure equilibration whereas smaller differences will not (Gaihede et al. 2010).

Finally, there is the important role of gas exchange and the ME cleft mucosa. The gases in the ME cleft are in equilibrium with the gases dissolved in the venous blood perfusing the mucosa. This equilibrium is disturbed whenever the ET opens and small amounts of gas are introduced from the nasopharynx. This leads to a continuous net absorption of gases before a new equilibrium is reached, which ultimately leads to the formation of underpressure in the ME cleft. This process is discussed in further detail in Sect. 5.4.

The rate at which this process occurs depends on several parameters such as the solubility of the gases, their diffusion coefficient, the amount of blood that can absorb gas, the effective surface area of the blood vessels, the effective tissue thickness, and other physical parameters of the gasses and the vessels. In this way, the process can be limited either by the diffusion rate or by the perfusion rate of the mucosal blood supply. Which of the two is the limiting factor is still a point of ongoing discussion. If diffusion is the limiting factor, then gas exchange is a constant process that cannot be changed on a short time scale by the body itself. If perfusion is the limiting factor then, in principle, an active control mechanism could exist that may change the perfusion rate of the mucosa by contraction or dilatation of blood vessels. Changes in perfusion may therefore actively influence the gas exchange: if blood flow increases, larger amounts of gas can enter or leave the ME cleft per unit of time.

Apart from gas exchange, swelling and de-swelling of the mucosa may also influence ME pressure by changing the effective ME gas volume (Magnuson 2003). This process is clearly perfusion bound. It may act quickly and therefore also has the potential to be part of a regulatory mechanism.

ET function is triggered by either voluntary or involuntary actions. Pressure regulation by gas exchange and mucosal congestion might also be an actively controlled mechanism. For active feedback mechanisms to exist, the ME needs to have some way of detecting the presence of pressure differences between it and the

environment. Stenfors et al. (1979) have argued that the pars flaccida may act as a pressure receptor, a view supported by the discovery of nerve endings in the pars flaccida (Lim 1970). If such mechanoreceptors are present, they may constitute the afferent components in an active feedback system that controls ME pressure. Recent work has shown distinct brain stem activation, in response to static pressure changes, that demonstrates that distinct afferent pathways exist that can be related to such actively controlled feedback regulation of ME pressure (Sami et al. 2009). If such an overall control mechanism can be demonstrated, it may have an important impact on future clinical management of those ME diseases that are connected to ME pressure deregulation.

5.2 Clinical Importance of ME Pressures

ME pressure is an important pathogenic factor which plays a major role in diseases of the ME, and can cause hearing loss and need for ME surgery. This section reviews a series of ME diseases and related sequelae in which negative ME pressure plays a crucial role.

5.2.1 Otitis Media with Effusion

In childhood, negative ME pressure is frequently encountered in cases of otitis media with effusion, with 80 % of all children experiencing at least one episode before the age of 4 years (Zielhuis et al. 1990). Traditionally, the pathogenic events have been explained by the ex vacuo theory proposed by Politzer (1867), where gas absorption in the ME cavity is insufficiently counterbalanced by a decreased gas supply resulting from an impaired function of the ET. Due to the negative pressure, a fluid effusion is formed that fills the ME cavity and leads to the clinical symptoms of hearing impairment and a sensation of pressure in the ear in some cases. However, the exact details of pathogenic events in otitis media with effusion are still not clear. They may also be related to infection of the ME, so that in some cases the effusion can be interpreted as a resolution phase of acute otitis media (Sadé et al. 2003).

Treatments of otitis media by insertion of ventilation tubes into the TM are considered the most frequent surgical procedure in children in the Western world. In some countries, up to 28 % of children have surgery at least once before the age of 7 years (Gaihede et al. 2007). But although inserting ventilation tubes may restore hearing and prevent systematic negative ME pressure, there are often complications. Permanent perforation of the TM is a common finding after repeated insertions, especially for T-shaped tubes (a special type of ventilation tubes used for long-term treatment in recurrent cases). Up to 24 % of such cases experience

persisting permanent perforations, which subsequently need surgical reconstruction of the TM (Strachan et al. 1996).

Other common complications related to otitis media with effusion and treatments with tubes are TM sequelae such as myringosclerosis and atrophy, which are found in 88 % of ears (Gaihede et al. 1997). Myringosclerosis is formed by calcium deposits in the middle layer (lamina propria) of the TM leading to increasing stiffness, while atrophy is related to degeneration and depletion of the lamina propria fibers leading to decreased stiffness (Shanks and Shelton 1991). Whereas myringosclerosis has little clinical importance, because normal hearing is most often preserved, atrophy bears more important implications because it represents weak parts in the TM that are susceptible to pressure loading and formation of retractions pockets.

5.2.2 Tympanic Membrane Atrophy, Atelectasis, and Cholesteatoma

The TM consists of three layers: (1) an outer epidermal layer, (2) an intermediate lamina propria, and (3) an inner mucosal layer. In the pars tensa, the lamina propria contains an elaborate system of collagenous as well as elastin fibers that are arranged in both an outer radially oriented layer and an inner circularly oriented layer as well as intermediate parabolic fibers (Lim 1970). It is believed that this structural arrangement forms the mechanical skeleton of the TM, and that this is important for both its mechanical and acoustic properties (Fay et al. 2006). In the lamina propria of the pars flaccida the fibers are more abundant and have a more irregular and loose organization, whereas the organization of the superficial epidermal and mucosal layers is similar to that of the pars tensa (Lim 1970).

The exact events leading to atrophy and degeneration of the lamina propria are not known. One possibility, suggested by Tos et al. (1984), is that negative ME pressure represents a long-term mechanical loading of the TM resulting in degeneration of fibers. They based their hypothesis on the demonstration of a correlation between the duration of periods with negative ME pressures and the presence of atrophy in children suffering from otitis media with effusion.

Moreover, static experimental pressure loading of the TM has demonstrated that larger deformations are found in areas where retraction pockets are frequently formed (von Unge et al. 1999). Based on these observations, pressure loading leads to a progressive thinning in these areas and to disintegration of the lamina propria resulting in atrophy (Ars et al. 1989). Alternately, intrinsic factors such as increased stress due to inflammatory changes and swelling of the TM outer layers may also contribute to mechanical strain with depletion and degeneration of the fibers (Gaihede 2000).

Once atrophic parts of the TM have been formed, and the original stiffness is lost, the TM becomes less resistant to further pressure loads. This provides the basis

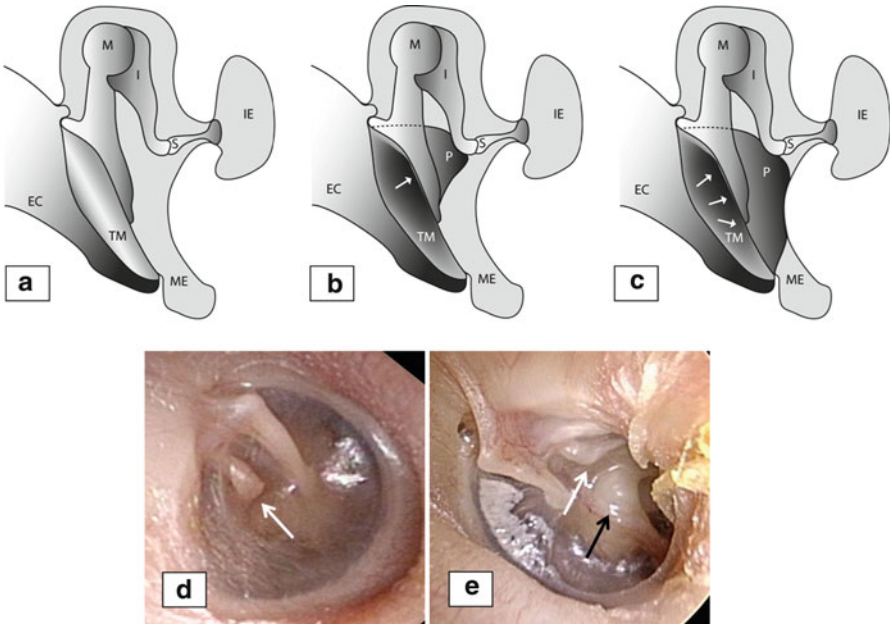

Fig. 5.2 Cross-sectional diagrams of the tympanic membrane (*TM*) and the middle ear (*ME*) cavity. (**a**) Normal TM position with normal aeration of the ME cavity. (**b**) Smaller distinct retraction pocket (*P*) of the posterior part of the TM with contact to the long process of the incus (*I*). (**c**) Pronounced retraction of the TM with contact to the long process of the incus and the medial wall of the ME cavity. *EC*, ear canal; *M*, malleus; *S*, stapes; *IE*, inner ear. The photographs (**d** and **e**) of TMs illustrate the two pathological diagrams (**b** and **c**); (**d**) shows a smaller localized retraction pocket in the TM with contact to the long process of the incus (*white arrow*), and (**e**) shows pronounced TM retraction with contact to the long process of the incus (*white arrow*) and adhesion of the TM to the inner wall of the ME cavity (*black arrow*)

for further progression of the atrophic degeneration and formation of retraction pockets, atelectasis of the TM, and cholesteatoma (Tos et al. 1984; Ars et al. 1989; Sadé 1993). Two examples of these conditions are illustrated by drawings and photographs of the TM shown in Fig. 5.2. Whereas in the first case (Fig. 5.2b, d) the TM shows only a minor retraction with contact to the long process of the incus and incudo-stapedial joint, the latter case (Fig. 5.2c, e) shows a pronounced retraction with contact to the inner wall of the ME cavity. Thus the TM has practically collapsed, illustrating an atelectasis of the posterior part of the cavity. Retraction and atelectasis with TM contact to the ossicles often result in bony erosion, which causes discontinuity and thus conductive hearing loss. In addition, the normal sound transmission of an atelectatic ME is also impaired owing to the mere collapse of the TM. Retractions of the pars flaccida as well as the posterosuperior part of the pars tensa are most commonly encountered.

Cholesteatoma represents a serious complication of retraction pockets in which accumulation of a whitish matrix of cellular debris causes recurrent infections and

drainage from the ear and its progressive growth in addition results in bony erosion. The pathogenic events have been described by Sudhoff and Tos (2000). Most frequently, the ossicles are affected, resulting in discontinuity of sound transmission and conductive hearing loss. Moreover, bony erosion may affect other structures in the ME such as the covering of the inner ear. If the inner ear is exposed by invasion of cholesteatoma then severe sensory-neural hearing loss or deafness is almost inevitable. These conditions represent irreversible changes of the ME structures, and surgical resection of the cholesteatoma is needed to prevent its further progression. In addition, the surgical procedures most often include reconstruction of both the TM and the ossicular chain to obtain a dry ear and to restore hearing (the so-called type II and III tympanoplasty), but normal hearing can rarely be obtained at this stage.

The postoperative course, and the long-term success of reconstructive surgery, following these conditions is also dependent on normal ME pressure. If impairment of pressure regulation continues after surgery then new retractions may form and create the basis for new disease. Recurrent cholesteatomas are quite frequent, especially in children, in whom it can amount to 20–25 % of the cases (Edelstein and Parisier 1989). Surgical techniques to prevent problems from sustained negative ME pressure, and thus to improve long-term results, include reconstruction of the TM with cartilage grafts, which have higher stiffness properties than traditional fascia and perichondrium grafts (Zahnert et al. 2000), as well as surgical obliteration of the mastoid, which may prevent sustained negative ME pressure (Takahashi et al. 2007; Vercruysse et al. 2008).

5.2.3 Summary and Future Research

The phenomenon of negative ME pressure is related to a major series of clinical ME conditions that lead to deteriorated hearing and demand surgical intervention and reconstruction of ME structures. Some cases involve simple closures of TM perforations, which generally are able to restore normal hearing, whereas others cause irreversible structural changes. The latter include cholesteatomas and many cases with atelectasis of the ME, in which permanently impaired hearing is inevitable despite optimal TM and ossicular reconstruction.

The behavior of retraction pockets is different. In some cases they remain stable for years, whereas in others they expand deeper into the ME and progress to cholesteatoma. Thus, it would be important to know when progression of the pathology can be expected. Clinical testing of both the topographical mechanical TM properties, as well as capabilities of ME pressure regulation, may reveal future correlations useful to identify such cases. Earlier surgical interventions can then be planned to prevent development of irreversible pathological changes and preserve normal hearing. Experimental studies have been reported in which focal changes in TM elastic properties could be measured quantitatively, but their clinical application requires further study (Dirckx and Decraemer 1992).

5.3 Measurement of ME Pressure

Measurements of ME pressure can be performed directly using various methods, and indirectly using tympanometry. Tympanometry has advantages in that it is a simple and fast procedure, and can be performed without any discomfort for the patient. These advantages make it especially good for measurements on children, in whom it has been employed in large clinical screening studies. Hence, tympanometry is very practical and not limited by ethical restrictions related to direct methods for determination of ME pressure. However, the indirect principle of tympanometry includes a number of methodological limitations and possible measurement errors, especially in diseased ears in which determination of the ME pressure is particularly relevant. This section describes measurements of ME pressure using tympanometry and explains some of these limitations. In addition, methods for direct measurements are shortly reviewed.

5.3.1 Basic Principles and Limitations of Tympanometry

Tympanometry is based on impedance measurements introduced by Metz (1946). Later, Thomsen (1960) described the first tympanogram that recorded the relationship between continuous changes in the ear canal pressure and the impedance. Thomsen demonstrated that the impedance was minimal when the ear canal pressure was equal to the ME pressure. Thus, the ME pressure could be determined from the impedance dip of the tympanogram.

In modern tympanometry the admittance is measured rather than impedance, and a low-frequency probe tone is used so that the compliance component of the admittance can be determined. Shanks and Shelton (1991) provided a review of the basic principles of modern tympanometry. In Fig. 5.3, a normal tympanometric recording is illustrated, in which compliance is depicted as a function of the ear canal pressure. This tympanogram also demonstrates that different curves are obtained for different directions of pressure change, that is, from positive toward negative pressure (negative pressure sweep) and vice versa (positive pressure sweep). For a negative pressure sweep the determination of ME pressure yields a value that is more negative compared with a positive pressure sweep. The corresponding peak pressure difference is illustrated in Fig. 5.3. This peak pressure difference reflects an error of measurements, in which the actual ME pressure probably corresponds to the mean of the two pressure peaks (Decraemer et al. 1984; Hergils et al. 1990).

The peak pressure difference can be explained by phase delay and hysteresis. Phase delay is an instrumental factor related to each instrument, but it can probably be considered negligible in most modern tympanometers (Therkildsen and Gaihede 2005). Hysteresis reflects the viscoelastic properties of the TM and the ME system. In normal ears hysteresis is negligible because it corresponds to only 10–15 daPa

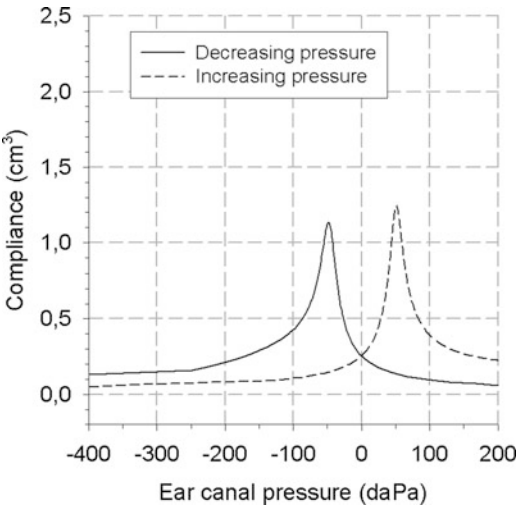

Fig. 5.3 Tympanometric measurements recorded in both negative (+ to −) and positive (− to +) directions. For the negative pressure sweep peak compliance (admittance) appears around −50 daPa, thus indicating a ME pressure of −50 daPa, while for the positive pressure sweep at + 50 daPa. The peak pressure difference (*PPD*) illustrated here amounts to 100 daPa

(Decraemer et al. 1984; Therkildsen and Gaihede 2005). In contrast, in diseased ears with ME effusion the peak pressure difference may increase, so that it introduces an error of greater than 200 daPa (Gaihede et al. 2005).

Further sources of measurement errors include the volume displacement of the TM related to the procedural ear canal pressure changes during tympanometry. Because the ear canal pressure variation displaces the TM, the actual ME pressure is affected. This effect is most prominent in ears with a small ME cleft volume and a flaccid TM (Flisberg et al. 1963; Ingelstedt et al. 1967). Several clinical studies have shown a good agreement between tympanometric estimates and direct measurements of ME pressure; however, these studies are limited in that they were performed only in normal ears, with normal sized ME clefts and normal TM mobility (Thomsen 1960; Takahashi et al. 1987a; Hergils et al. 1990).

Mechanical model experiments have been used to analyze the effect of ME cleft volume on the tympanometric estimate of ME pressure. These experiments suggest that the tympanometric ME pressure approaches $-\infty$ daPa when ME volume approaches 0 cm^3 (Gaihede 2000). Thus, high negative ME pressures can be obtained as an artifact of tympanometry merely due to the depletion of the air volume, which corresponds not only to the situation of a small ME cleft volume per se, but also to cases with ME effusion.

Monitoring changes in ME pressure over time is essential to the understanding of the overall regulation of pressure. Usage of tympanometry may be justified in such studies because the differences between pressure values are important, and any errors of measurements can be assumed to be the same in each recording. However, long-term monitoring of ME pressure using tympanometry is not very practical, and 24-h measurements have been reported in only one study (Bylander et al. 1985). Moreover, the temporal resolution is very poor, as measurements have been reported only at intervals of 3–15 min (Bylander et al. 1985; Grøntved et al. 1989).

Altogether, tympanometric measurements of ME pressure in normal ears have shown good agreement with direct measurements. However, results should be interpreted with caution, especially in diseased ears in which the combination of increased hysteresis and depletion of ME cleft air volume is likely to result in a highly inaccurate estimate of ME pressure. According to the ex vacuo theory described by Politzer (1867), ME effusion has traditionally been interpreted as a transudate resulting from negative ME pressure and not an exudate due to inflammation. However, ME transudate formed due to a hydrostatic pressure difference between the air and blood phase depends on a negative pressure of 50–90 daPa, whereas an exudate can be formed due to inflammation only. Thus, knowing the exact ME pressure is important for a correct interpretation of pathologic events (Sadé and Ar 1997), and this can be obtained only by direct measurements.

5.3.2 Direct Measurements of ME Pressures

Direct methods for clinical measurements of ME pressure include puncturing of the mastoid (Flisberg et al. 1963; Hergils et al. 1990), puncturing of the TM (Buckingham and Ferrer 1973; Sadé et al. 1976), and insertion of a pressure transducer through the ET (Takahashi et al. 1987a). These methods may be more accurate than tympanometry, but they are also limited by various practical problems and obvious ethical restrictions. Moreover, these methods are not suitable for monitoring changes in ME pressure on a day-to-day basis, which is necessary for analysis of the overall and long-term regulation of the ME pressure.

Other researchers have described direct clinical methods suitable for long-term ME pressure measurements. Tideholm et al. (1996) employed a method in which a pressure transducer was incorporated into an ear mold and the pressure could be measured through the ear canal in subjects with either a TM perforation or a ventilation tube; full 24-h monitoring was achieved illustrating normal pressure variations (Tideholm et al. 1998). However, the use of TM perforation, or a ventilation tube, prevents any pressure loading of the TM. Thus, activation of TM mechanoreceptors is avoided, so that possible afferent neural input to regulatory brain stem centers is impaired. Consequently, analysis of overall pressure regulation seems limited.

In more recent clinical experiments, a small pressure transducer was connected to a catheter that was inserted into the mastoid. A recording unit carried by the subject sampled pressure data at a high frequency (0.1 Hz) with the capacity for 48-h recording. Thus, long-term monitoring was possible during normal daily activities (Jacobsen et al. 2007). Because the catheter was inserted into the mastoid, the TM remained intact. Hence, important TM-related neural stimuli remained intact. Figure 5.4 illustrates an example in which a subject was exposed to changes in ambient pressure due to an elevator ride. The results clearly show how changes in ME pressure correlate with changes in altitude. Thus, relatively small variations in ambient pressure, which people are normally unaware of,

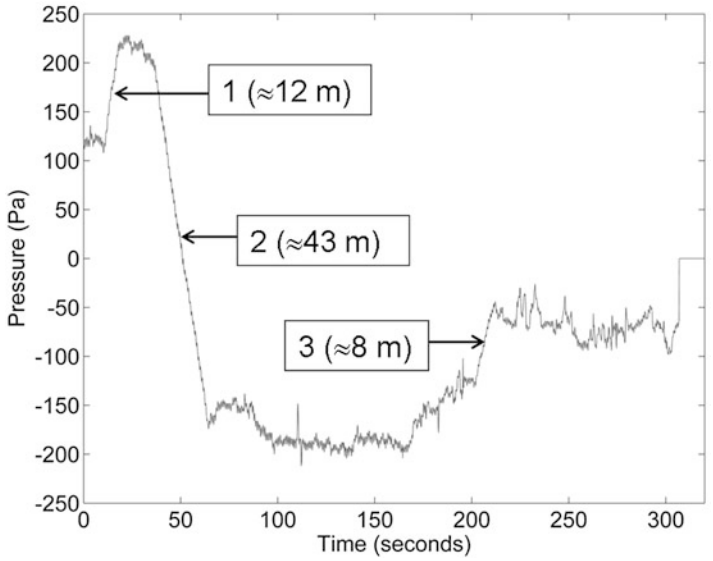

Fig. 5.4 ME pressure changes in a normal human subject in response to changes in altitude. The experiment included three elevator rides illustrated by the *straight lines* pointed out by *arrows*: (1) from the 7th floor to the 10th floor ($\Delta P \approx +100$ Pa); (2) from the 10th floor to the basement ($\Delta P \approx -375$ Pa), and (3) from the basement to the 1st floor ($\Delta P \approx +80$ Pa). Estimated differences in altitudes are indicated. ET openings were not observed during this experiment

can actually be measured. However, the analysis of such detailed variation of ME pressure for long periods of time is very complicated and still awaits future studies (Gaihede et al. 2010).

5.3.3 Summary and Future Research

In summary, tympanometry is a widely used clinical method for determination of ME pressure but it contains methodological limitations decreasing its accuracy in diseased ears. It may be reliable in cases in which temporal changes in pressure are studied and compared, but the time resolution is not satisfactory. Ultimately, direct pressure measurements with an intact TM should be performed over longer periods with methods employing high accuracy and sampling rate in order to analyze the overall ME pressure regulation.

5.4 ME Gas Composition and ME Gas Exchange

As shown in Fig. 5.1a, the ME cleft is a semirigid gas pocket that is closed most of the time. As such, gas diffusion between this (nearly) constant volume cavity and the blood leads to changes in pressure (Loring and Butler 1987). The passage of

each gas occurs according to its partial pressure gradient between these different compartments (Piiper 1965). The gas mixture contained in the ME cleft consists of O_2, CO_2, H_2O, N_2, and Ar. These are the same gases that are found in air, blood, and tissue. However, their partial pressures as well as their total pressures are different between the different compartments mentioned previously, as reviewed by Sadé and Ar (1997).

Today it is still not clear whether the exchange of the different gases in the ME is limited by blood perfusion or by diffusion through the mucosa (Marcusohn et al. 2010). A debate exists regarding the role of the TM as well, as explained in the text that follows.

5.4.1 ME Gas Composition

Several researchers have studied ME gas composition in several species (cat, dog, guinea pig, chinchilla) as well as in humans (Ostfeld et al. 1980; Hergils and Magnuson 1990; Sadé and Luntz 1993 and references therein). Riu et al. (1966) used gas chromatography to obtain data on the gas composition of the human ME and found that it contained 9.5 % volume O_2, and 5.5 % volume CO_2.

Results obtained by Ostfeld et al. (1980) in dogs (using gas chromatography) were within the range of values previously obtained in humans (Ostfeld et al. 1980). Felding (1998), using gas electrodes for sampling, reported similar results for normal ears who found partial pressures of $O_2 = 5.7$ % and $CO_2 = 6.6$ %, and concluded they are close to equilibrium with mixed or local ME venous blood ($O_2 = 5.3$ % volume and $CO_2 = 6.1$ % volume). In other studies demonstrating lower CO_2 and higher O_2 values, samples were probably contaminated with atmospheric air. Hergils and Magnuson (1990) emphasized the major difficulty in studies of ME gas composition, namely the ability to obtain samples without contaminating them with ambient air.

Sadé et al. (1995) measured the gas composition in the MEs of guinea pigs continuously using mass spectrometry. They observed increases in P_{CO_2} and decreases in P_{O_2} until the system reached a steady state, and reported that the steady-state values measured in their experiments were similar to results obtained in previous studies by a single measurement. As described previously, these continuous gas composition measurements also provided information on the kinetic pattern of ME gas exchange—a topic explained further in the next section.

5.4.2 Overview of Experiments on Gas Exchange

ME gas exchange has been studied in different animal models as well as in humans. Pressure changes and/or volume changes were measured using various methods.

Ingelstedt and Jonson (1966) connected a pressure transducer directly to the mastoid and a flowmeter to the ear canal of normal subjects. Using their setup they were able to observe and quantify the behavior of the ME for a few hours. They described periods in which underpressure was slowly built and saw how these intervals were interrupted during pressure equilibration events where the ET opened and the TM returned to its normal position. Using these results, they estimated that the ME gas absorption rate in normal human ears is 1–2 mL/day.

In the study by Elner (1972) the subjects did not swallow for 5–10 min. When the ET finally opened and the TM returned from retracted to normal (neutral) position, the volume displacement was determined. Elner's calculations (1972) gave the rate of gas absorption from normal MEs as 0.7–1.1 mL/day.

In various studies performed in animal models (e.g., Doyle et al. 1995, 1999; Kania et al. 2004; Marcusohn et al. 2006), and in humans (Aoki et al. 1998; Uchimizu et al. 2005), pressure or volume changes were monitored after the normal gas composition of the ME was changed. A typical curve included two phases (Marcusohn et al. 2006): In the first phase, "a," an exponential increase (in gas volume) was observed, whereas in the second phase, "b," a gradual decrease was seen. It was assumed that entrance of the very soluble CO_2 (as compared to O_2 and N_2) into the ME from the mucosal blood caused the fast (pressure or volume) increase in the first phase, whereas diffusion of N_2 from the ME to the blood (Kania et al. 2006) was assumed to be the governing factor in the second phase.

5.4.3 Perfusion/Diffusion Limitations of Gas Exchange

The question of whether perfusion or diffusion is the main limiting factor in ME gas exchange is still open. Van Liew (1962) studied gas exchange in subcutaneous gas pockets. His results indicated that the exchange of CO_2 and O_2 was limited by diffusion, while the exchange of N_2 was at least partially limited by perfusion, in accordance with conclusions of previous studies (Van Liew 1962).

Piiper et al. (1962) also addressed the role of perfusion in N_2 exchange. According to their study, in which they used subcutaneous gas pockets, the main factor that governs N_2 exchange is diffusion. Doyle et al. (Doyle and Seroky 1994; Doyle et al. 1995, 1999) studied the exchange of gases in the ME of monkeys. They concluded that the exchange of CO_2 and O_2 is limited by diffusion but the exchange of N_2 is limited by perfusion. Clearly there is not yet agreement among all experimental findings.

Marcusohn et al. (2010) tried to determine the limiting factor of CO_2 exchange using phase "a" data obtained from rabbits and rats and calculations of mass specific cardiac outputs in these animals. They found that the ratio [mass specific initial flow rate in rabbits]/[mass specific initial flow rate in rats] was similar to the ratio [mass specific cardiac output in rabbits]/[mass specific cardiac output in rats].

Under reasonable assumptions this result indicates that the exchange of CO_2 in the ME of mammals is limited mainly by perfusion.

In conclusion, significant evidence supports the notion that CO_2 exchange is mainly perfusion limited, yet other studies still support the idea of a diffusion-limited process. The discussion regarding the different gases is ongoing, and more experiments are needed to draw final conclusions. This debate is highly important because blood perfusion can change quickly (due to constriction or dilatation of vessels), whereas diffusion can change only on much longer time scales (due to thickness changes of the mucosa). A perfusion-limited system can therefore be part of a fast-acting pressure regulation mechanism.

5.4.4 Gas Exchange Across the Tympanic Membrane: Fact or Artifact?

Previous studies reported conflicting results regarding another basic question in ME physiology, namely, whether or not the TM plays an actual role in gas exchange. Elner (1970) studied human TM preparations (taken from cadavers with normal ears) in a diffusion chamber. According to their report, CO_2 diffused through the TM at a very slow rate. An in vivo study by Riu et al. (1966) indicated that there was no exchange (or very low level of exchange) of xenon through the TM. In a more recent study, Yuksel et al. (2009) analyzed samples of gas from a sealed part of the ear canal adjacent to the TM using a mass spectrometer. Their results support the idea that the TM is somewhat permeable to CO_2 and O_2. They also refer to other studies in which trans-TM gas exchange was reported. Still, if there is any gas exchange through the TM, the effect is far smaller than the exchange through the mucosa, so trans-TM gas exchange is not a main factor in ME pressure regulation.

5.5 Tympanic Membrane Deformations as a Pressure Regulator

When the eardrum is deformed due to pressure loading, it changes the volume of the ME cleft. Such volume change in turn has an influence on pressure. In this way, eardrum deformation reduces pressure changes, giving the eardrum a possible regulative role. Such a regulative role has been attributed to the pars flaccida because it can move very easily. In this section quantitative results of eardrum deformation are shown and their contribution to pressure regulation is discussed.

5.5.1 Pressure Regulation by Tympanic Membrane Volume Displacement

When the ET is closed, the ME cleft can be regarded as a closed volume containing a fixed amount of gas. As discussed in the preceding sections, the amount of gas does change over time due to the gas exchange mechanisms with the blood in the mucosa, but over short periods of time the amount of gas enclosed in the ME cavity can be regarded as constant. When the ambient pressure changes, the pressure in the ear canal, $P_{EC,}$ will change in the same way, resulting in a pressure gradient $P_{ME} - P_{EC}$ over the TM, where P_{ME} is the pressure in the ME cleft. The pressure load will displace the TM, thus compressing or expanding the gas in the ME. This compression or expansion increases or decreases ME pressure, thus reducing the pressure gradient over the TM. Displacements of the TM may therefore act as a regulative mechanism of ME pressure. Of course, the displacement itself also results in a stress on the TM. Ever since Shrapnell's observations on the pars flaccida, the idea has existed that this part of the TM could act as a pressure regulator by changing ME volume, and thus reducing the pressure load on the pars tensa (Shrapnell 1832).

Elner et al. (1971a) have presented clinical experiments in which ear canal air flow was measured to calculate the TM volume displacement as a function of pressure variations (volume–pressure relationship). In similar clinical experiments, Gaihede and Kabel (2000) presented measurements of ear canal pressure as a function of TM volume displacements (pressure–volume relationship). In both of these studies the volume displacements involved the entire TM. A more detailed approach has been reported by Dirckx and Decraemer (1992), who used Moiré profilometry, an optical method, on human cadaver temporal bones to measure the actual displacement of the TM over its entire surface. From such optical measurements TM volume displacements can be calculated also for the pars flaccida separately. Figure 5.5 shows the results of these experiments, and it is clear that the methods agree well for the entire TM. The graph also shows the results obtained separately for the pars flaccida, and it is immediately clear that its volume displacement is about 10 times smaller than the displacement of the entire TM. This observation suggests that the regulatory capacity of the pars flaccida, at least in humans, is limited.

For higher pressure loads, volume displacements of both the entire TM and the pars flaccida show a considerable asymmetry as a function of positive and negative pressure. Larger displacements were observed as the membrane was pushed laterally, as compared to medial displacements at the same pressure. Thus, at $P_{ME} - P_{EC} = +1.5$ kPa the TM volume displacement was about 20 μL, while at $P_{ME} - P_{EC} = -1.5$ kPa the displacement was only 15 μL. This asymmetry is probably connected to the conical and bent surface shape of the TM. For an outward motion, the TM can bulge and the manubrium can move rather easily. For an inward motion the shape of the slightly curved TM can only change into a straight-walled

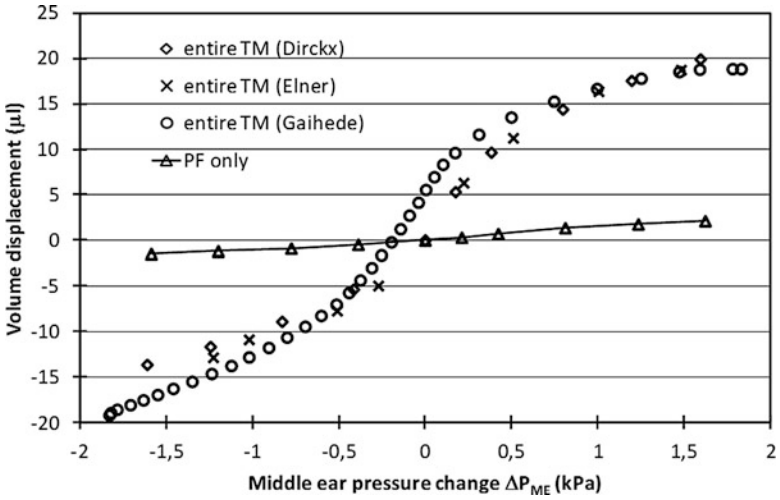

Fig. 5.5 Volume displacement of entire human TM from previous studies (*diamonds, crosses,* and *dots*) and of the TM pars flaccida PF separately (*triangles*). Data measured by Dirckx et al. (1998) originate from a human temporal bone, whereas data from Elner et al. (1971a) and Gaihede and Kabel (2000) are based on clinical experiments. (Data reproduced from Dirckx and Decraemer 1998, with kind permission of S. Karger AG; data reproduced from Gaihede and Kabel 2000, with kind permission from Kugler Publications, Amsterdam)

cone. It needs to be stretched for the manubrium to move further inward. The shape changes of the TM under pressure have been measured in full field using moiré profilometry (Dirckx and Decraemer 1992), and the conical shape of the TM plays an important role in the highly asymmetric motion of the manubrium for over- and underpressures.

The actual pressure load on the TM depends not only on volume displacement, but also on the amount of gas in the ME cleft. Using estimations of ME cleft volume, the relative pressure regulative capacity of TM and pars flaccida can be calculated. The volume of the ME in humans is rather constant over individuals, whereas the volume of the mastoid has much larger variability. Flisberg et al. (1963) calculated volume displacements of the intact TM in normal ears using manometers. One manometer was connected to the ear canal and another was connected to the mastoid (through a cannula). Pressure changes were produced using a syringe that was connected to the system between the manometer and the mastoid cannula. The effects of these changes were measured by the first manometer situated in the ear canal, and were then converted to TM volume changes. The maximal values for TM displacement as calculated by Flisberg et al. (1963) were 25–40 µL, which is in fair agreement with the 20 µL found in direct optical measurements on temporal bones (Dirckx and Decraemer 1992).

5.5.2 Measurements on Human Temporal Bones

Relative pressure compensation can be calculated in the following way. When the TM is in its resting or neutral position, when ear canal pressure P_{EC} is equal to ME pressure P_{ME}, the pressure in the ME is related to ME cleft volume V_{ME} and temperature T of the ME by the ideal gas law, or Boyle's law:

$$P_{ME} \times V_{ME} = \text{constant} \tag{5.1}$$

As stated before, it is a fair assumption to regard the amount of gas being constant over short periods of time. If the TM is now displaced, it will cause a volume change ΔV of the ME cleft. According to the gas law, this will in turn cause a change in ME pressure ΔP_{ME}. Assuming that the compression or expansion of the ME gas is isothermic, ME pressure will change to a value $P'_{ME} = (P_{ME} + \Delta P_{ME})$ determined by:

$$(P_{ME} + \Delta P_{ME}) = P_{ME} \times V_{ME}/(V_{ME} + \Delta V_{ME}) \tag{5.2}$$

The relationship between ΔV_{ME} and ΔP_{ME} is given by the experimental results shown in Fig. 5.5. These results were obtained from optical deformation measurements on pars tensa and pars flaccida in a normal human temporal bone (Dirckx and Decraemer 1991). In the experiments that yielded Fig. 5.5, ME pressure was changed by injecting gas into the ME and allowing the TM to move freely. In reality, it is the pressure in the ear canal that changes, thus displacing the TM and compressing (or expanding) the fixed amount of gas in the ME cavity. So the ear canal pressure will be equal to the sum of the ME pressure and the additional pressure needed to displace the TM and compress the gas present in the ME. The change in ear canal pressure ΔP_{EC}, which will cause a TM volume displacement equal to ΔV_{ME}, is calculated in the following way:

$$\Delta P_{EC} = \Delta P_{ME} + (P_0 \times \Delta V_{ME})/(V_{ME} + \Delta V_{ME}) \tag{5.3}$$

Here P_0 is the ambient pressure in the ear canal for the TM in its neutral position. Using this equation, Fig. 5.5 is reworked to a graph with ear canal pressure on the horizontal axis.

Next, a definition for the pressure regulative capacity of the membrane is needed. The relative pressure compensation due to TM displacement can be given as the difference between the pressure change ΔP_{ME} in the ME divided by the difference change ΔP_{EC} in the ear canal:

$$\Delta P_{ME}/\Delta P_{EC} \tag{5.4}$$

Using these equations and the experimental data shown in Fig. 5.5, one can now calculate the relative pressure compensation capacity of the TM and the pars

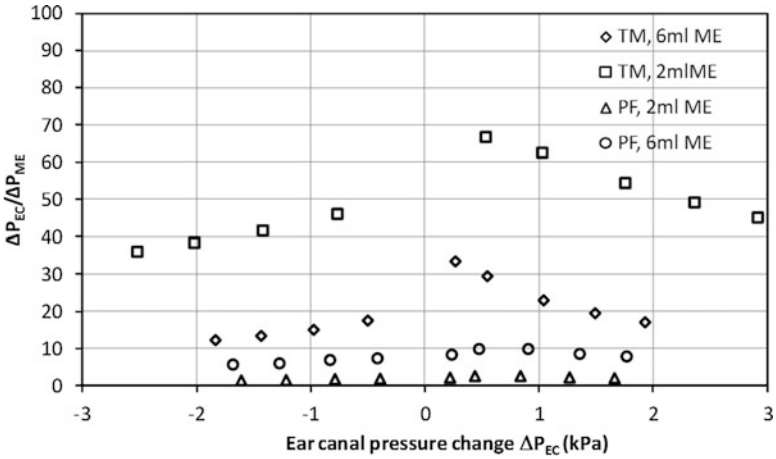

Fig. 5.6 Pressure regulation caused by displacement of the entire TM (*squares* and *diamonds*) and of the TM pars flaccida (*PF*) only (*crosses* and *triangles*) calculated for a ME volume of 2 mL (*squares* and *crosses*) and of 6 mL (*diamonds* and *triangles*). The pressure regulative capacity $\Delta P_{ME}/\Delta P_{EC}$ is significantly larger in ears with small ME volume. The contribution of the pars flaccida is marginal as compared to the entire TM (Data reproduced from Decraemer and Dirckx 1998, with kind permission of S. Karger AG)

flaccida under different circumstances. Figure 5.6 shows the result obtained at normal body temperature (37 °C or 310 K), for a ME cleft volume of 6 and 2 mL, respectively (6 mL is regarded as a normal ME cleft volume) (Elner et al. 1971a; Cinamon and Sadé 2003).

If the TM would be completely rigid, no pressure compensation would take place and $\Delta P_{ME}/\Delta P_{EC}$ equals 0 %. For a perfectly flaccid TM, ME pressure would always be exactly equal to ear canal pressure and $\Delta P_{ME}/\Delta P_{EC}$ would be 100 %. Figure 5.6 shows that in an ear with a normal large volume, TM displacement compensates some 10–35 % of the external pressure changes, while in an ear with reduced gas content the compensation effect reaches 30–65 %. As the displacement of the TM is a nonlinear function of pressure, the compensation effect is strongest for small pressure differences. Figure 5.6 also shows that the compensating capacity of the pars flaccida is marginal. In an ear of 6 mL volume, the pressure compensation due to the pars flaccida displacement is not larger than a mere 3 %.

From these results it is clear that volume displacement of the TM does indeed have some compensation effect on pressure differences between the ME and the ear canal, but the effect is rather limited and present mainly at very small pressures. The pars flaccida provides only a marginal contribution to pressure compensation. Reducing ME cleft volume from 6 to 2 mL doubles the pressure compensation effect, which might have useful implications on management procedures for ears with recurrent problems of impaired pressure regulation (see Sect. 5.7.1).

According to clinical observations reported by Luntz et al. (1997), pars flaccida retractions without retractions of the pars tensa are more frequent than the opposite situation. However, degeneration of the pars tensa discussed earlier, resulting in

atrophy, may result in weaker spots compared with the pars flaccida. Therefore, retraction of the pars tensa may sometimes occur without simultaneous retraction of the pars flaccida (Luntz et al. 1997).

5.5.3 Animal Experiments

In gerbils, pars flaccida deformation and volume displacement have also been measured as a function of pressure (Dirckx et al. 1997, 1998). The major part of the displacement is reached within a pressure range of just 0.2 kPa, and beyond 0.4 kPa hardly any change is observed. The contribution of the pars flaccida to ME pressure regulation in gerbils is thus limited to a mere 200 Pa range. In three animals, maximal volume displacement at negative ME pressure varied between −0.476 and −0.301 μL between ears, and maximal volume displacement at positive ME pressure ranged from 0.239 to 0.358 μL. The volumes of the MEs were also measured varying between 250 and 270 μL. In any case, maximal volume displacement of the pars flaccida was smaller than 0.2 % of ME cleft volume. From these observations it is clear that even if the pars flaccida were perfectly flaccid, it cannot compensate for changes of more than 0.2 % of ambient pressure or 20 Pa.

The results obtained in these studies do not, of course, contradict a possible pressure regulative role of the pars flaccida at the very lowest pressures. To investigate this, it is necessary to see how the trans-tympanic pressure changes under very small pressure variations in the ear canal. Of course, in gerbil displacement of the pars tensa will also contribute to pressure buffering, but this has not been measured in detail. The main result of animal measurements is that the pars flaccida certainly is not the main pressure regulator, as was suggested in the past.

5.5.4 Summary and Future Research

Displacements of the TM due to pressure differences between the ear canal and the ME have some compensating effect on these pressure differences, but the effects are limited. There is no evidence that the pars flaccida has a significant function in ME pressure compensation, except possibly in the extremely small pressure range of a few tens of Pa's. In that pressure range the pars flaccida may react very quickly to sudden pressure changes, and could certainly also have a function in shunting ultralow- and low-frequency sound. Moreover, the pars flaccida and the pars tensa have been shown to contain nerve endings, so in addition of being a pressure regulator, the TM and especially the pars flaccida may act as a pressure detector involved in overall ME pressure regulation. Further research on TM innervation and on central control of ME pressure is needed to investigate this possibly very important role of the pars flaccida.

5.6 The Eustachian Tube

For a long time, the ET has been considered to be the prime active component in ME pressure regulation, and its functioning has been the subject of research for many years. The problem is that the clinical course of retraction pockets does not correlate at all with results of ET function tests. In this section a brief overview is given of findings with respect to ET function.

5.6.1 Anatomy

The ET connects the ME with the nasopharynx. The length of the ET is about 31–38 mm (Bluestone and Doyle 1988). It consists of a bony part, of about one third of its total length, as well as a cartilaginous part, of around two thirds of its length (Prades et al. 1998). The open bony part is connected at one end to the ME, and at its other end to the cartilaginous part through a narrow (~ 2–3 mm high, ~ 1–1.5 mm wide) isthmus (Magnuson and Falk 1988). The growth pattern of the ET lumen has been described by Luntz and Sadé (1988). Results obtained in these studies contradicted the previously held notion that the ET is wider in children and infants than in adults. Thus, other than describing the general growth of the ET lumen with age, Luntz and Sadé (1988) also indicated that the cartilaginous part grew to a greater extent as compared to the bony part.

The main peritubal muscles are the tensor veli palatini and the levator veli palatini. The tensor veli palatini is connected to the sphenoid, the soft palate, and the lateral lamina of the cartilaginous part of the ET. The levator veli palatini is connected to the petrous apex, the soft palate, and the ET (Bluestone and Doyle 1988; Prades et al. 1998).

5.6.2 Function

Bylander (1986) referred to three functions of the ET: equilibration of pressure, drainage or clearance of the ME, and protection of the ME. A good review of the clearance as well as the pressure equilibration functions was given by Sadé and Ar (1997). This section focuses mainly on the ET as a pressure equilibrating organ.

Several methods to test ET function have been proposed. Elner et al. (1971b) cited previous authors who used several different methods to test the ET function by recording TM displacement or ME pressure. In addition to methods involving intra-ET sound conduction, contrast media (radiographic studies) or tracer solutions have been used (Ingelstedt and Örtegren 1963). Recently, Swarts et al. (2011) reported normative values of ET function tests (force response test, inflation and deflation tests, “sniff” test, and Valsalva) obtained from healthy adults. Bylander et al. (1981)

studied the function of the ET in normal children and adults using tympanometry and compared their findings to those obtained by Elner et al. (1971b) in normal adults. Their findings indicate that the muscular opening function of the ET improves with age until adulthood (Bylander et al. 1981). Takahashi et al. (1987b) calculated a characteristic parameter called tubal compliance index. For this parameter they did not find any difference between normal children and adults. However, when subjects who had otitis media with effusion were examined by them, it seemed that the tubal compliance index was higher in children with otitis media with effusion than in normal subjects. On the other hand, the tubal compliance index was lower in adults, who suffered from this pathology, than in normal subjects. Thus, according to Takahashi et al. (1987b), it seems that children who suffer from this pathology have compliant ETs, in contrast to adults with otitis media with effusion who have rigid ETs.

Finally, the effect of deglutition events has been investigated. Different studies indicate that the amount of gas that passes between the nasopharynx and the ME during effective deglutition events (events in which the ET opens) is very small, as compared to the volume of the ME cleft. According to Elner (1977) the amount of gas that enters the ME in a deglutition event is ~1 μL. A more recent study found this amount to range between 0.79 and 2.79 μL (Mover-Lev et al. 1998). These findings indicate that deglutition cannot significantly change ME gas composition.

Harell et al. (1996) and Hergils and Magnuson (1998) measured the gas composition of the nose and the nasopharynx in order to estimate the composition of the gas that enters the ME during a deglutition event. They found that it was similar to the gas composition of expired air. Hence, it was closer to ME gas composition than to air. In a study performed by Mondain et al. (1997) on normal subjects, it was found that the ET was open for about 430 ms during effective deglutition events. The opening frequency of the ET was 1–2 times/min. In summary, the composition of the gas entering the ME during deglutition events is rather close to the composition of the gas present in ME, and the amount of injected gas is very small.

5.6.3 The Role of the Eustachian Tube in ME Aeration

Holmquist (1978) suggested that an active "pumping" mechanism may exist, whereby gas passes from the nasopharynx into the ME through the ET. This notion was further supported by Sadé et al. (2005). According to their findings, gas can enter the ME while pressure at both ends is equal. As this may indicate that an active mechanism exists in that direction, it was suggested as an explanation to the occurence of hyperectasis (Sadé 2001).

Honjo et al. (1983) recorded simultaneously electromyograms (EMGs) of the tensor veli palatini and the levator veli palatini as well as cineroentgenograms of the ET. They found that the distal and the proximal parts of the ET opened simultaneously, whereas a time lag was noted between the closures of each of these two parts. The proximal part (close to the ME) closed first, during the contraction of the

tensor veli palatini muscle. Afterwards, the distal part closed, during the contraction of the levator veli palatini muscle. Hence, their results suggest that an active mechanism, whereby gas is pumped out of the ME through the ET, may exist. Apart from this possible active function at small pressure differences, the ET also has a passive and protective regulation function, opening spontaneously at high positive ME pressures.

5.6.4 *Effects of Sleep and Body Position*

Mover-Lev et al. (1998) found that the swallowing rate decreased from about 30 events per hour to about seven events per hour in patients who fell asleep during their experiments. In these patients, who were seated, a decrease in ME pressure was recorded. They mentioned previous authors who reported a positive ME pressure during and after sleep in a horizontal position. Apparently body position has an important effect on ME pressure during sleep.

Tideholm et al. (1999a) who measured ME pressure continuously (for 24 h) and found that the mean number of ET openings were as follows: 9.4 per hour in the (awake) erect position, 8.4 per hour in the (awake) horizontal position, and, significantly lower, 3.2, per hour during sleep in the horizontal position. In their study, a higher ME pressure was recorded when subjects were asleep in the horizontal position, as compared to the other two conditions in which the subjects were awake (erect and horizontal positions) (Tideholm et al. 1999a). They suggested that this was due to entrance of CO_2 into the ME resulting from depression of respiratory function during sleep.

Bonding and Tos (1981) reported that in control group patients, who stayed in a horizontal position for 12–24 h after their operation, no significant change in ME pressure was observed. On the other hand, according to previous studies cited by them, increased hydrostatic pressure in the ET vessels and thickening of the mucosa led to reduced ventilation of the ME in this position. The role of the ME mucosal volume was emphasized by Gaihede and Kjær (1998) in a study performed on healthy (adult) subjects. According to them, an increase of mucosal volume was the reason for the observed increase in ME pressure in the horizontal position, as compared to the erect position. In summary, the pressure regulative role of the ET is rather limited and its effect is dependent on the interplay between several factors such as posture and sleep.

5.6.5 *Eustachian Tube Dysfunction/Occlusion*

Bonding and Tos (1981) discussed various situations that can lead to negative ME pressure. These included insufficient deglutitions (for instance, after tonsillectomy), obstruction of the ET orifice, and mucosal inflammation. In a study performed by

Kindermann et al. (2008) on children (2–12 years old), obstruction of the ET orifice was usually associated with negative ME pressure. In other cases in which the ET orifice was not occluded, normal ME pressures were usually demonstrated. The question of whether ET dysfunction/occlusion plays a role in ME pathologies was addressed by Sadé and Ar (1997) and in Sect. 5.2 of this chapter.

As noted by previous authors, the ET can also be permanently open or patulous (Sadé and Ar 1997). In some patients who suffer from this pathology, "fullness" of the ear and autophony are reported, although it is usually an asymptomatic condition (Pulec and Hahn 1970; Sadé and Ar 1997). In patients who have a patulous ET, the TM is usually normal, but sometimes it is atelectatic (Sadé and Ar 1997). A possible explanation for this interesting phenomenon has been suggested by Sadé and Ar (1997): It might be that a Bernoulli effect could lead to negative ME pressure in patients who have a patulous ET as the velocity of the air passing by an opening will cause underpressure.

Tideholm et al. (1999b) performed continuous ME pressure measurements (for 24 h) in subjects with patulous ETs. Interestingly, they found more pressure variability within the patulous ET group than within a normal group, which they studied previously. The pattern of pressure changes recorded in these experiments was significantly different between the groups. In the patulous ET group, an overall negative mean pressure was observed while subjects were sleeping in the horizontal position. The pressure recorded was variable between subjects (in some of them it increased, in other subjects it decreased). In addition, no significant pressure difference was found between the erect and the horizontal position at night in subjects with patulous ET. In contrast to these findings, increased pressure was recorded in most of the normal subjects during night. Hence, Tideholm et al. (1999b) concluded that a diagnosis of patulous ET is not necessarily associated with an ET that is constantly open.

5.7 The Mastoid Air Cell System

The exact role of the mastoid air cell system in pressure regulation of the ME remains unknown. The mastoid contains clusters of a large number of connecting air-filled cells. These cells lie behind the ME cavity and the ear canal, and extend toward the inferior tip of the mastoid (Fig. 5.7). Thus, the mastoid is relatively inaccessible, which may have limited basic research. The structure of the air cells can have an acoustic function, as the many surfaces help to break up acoustic vibration modes, prevent sharp resonances, and increase hearing sensitivity for low frequencies (Fleischer 2010). However, there are numerous clinical and structural observations, as well as more recent experiments, indicating an important and active role for the mastoid in pressure regulation.

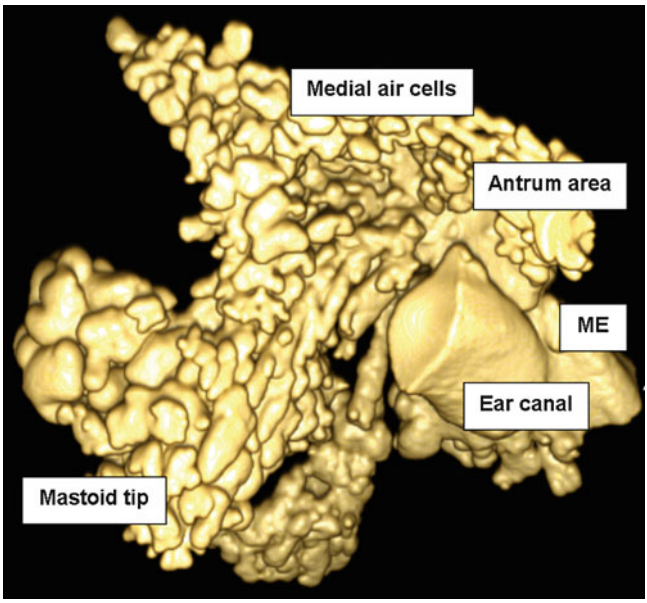

Fig. 5.7 The normal mastoid with clusters of air cells emerging from the posterior part of the *ME*. The ear canal is seen at the *right side* in the *middle* of the image. The image is based on a 3D reconstruction of a high-resolution clinical CT scanning, where the surface compact bone has been made transparent (Courtesy of Olivier Cros)

5.7.1 Pneumatization of the Mastoid and Clinical Observations

The air cell system is absent at birth, but develops during childhood by expansion of air-filled cells, mainly from the antrum; the normal extent of air-containing cells (pneumatization) of the mature system is reached at puberty (reviewed in Cinamon 2009). These developmental aspects are important, because there is a close clinical correlation between sclerotic changes with a decreased pneumatization of the mastoid, and chronic otitis media with formation of retraction pockets and cholesteatoma. Decreased pneumatization has been attributed to hereditary factors that increase the risk of development of chronic otitis media (Diamant et al. 1958); however, chronic otitis media itself may affect its normal development during childhood, leading to a decreased pneumatization (Tos and Stangerup 1984).

Further clinical evidence for the mastoid role in pressure regulation relates to the success of postoperative courses of surgical reconstructions; in patients with smaller and diseased sclerotic mastoids the recurrence risks of retractions and cholesteatoma are higher. Based on these observations, many centers apply surgical obliteration of the mastoid. The basic idea is that the diseased mastoid contributes to an impaired pressure regulation, and by its occlusion the formation of new underpressures can be prevented. Moreover, the pressure regulation capacity of the TM is favored by a smaller ME cleft (please refer to Sect. 5.5.2 in this chapter). Hence, mastoid obliteration has significantly reduced the risks of recurrence of cholesteatoma (Takahashi et al. 2007; Vercruysse et al. 2008).

5.7.2 Structural Properties of the Mastoid

The structure of the mastoid bears implications for its function. The volume of the ME cavity itself is rather small, around 0.5–1 mL (Sadé 1997; Alper et al. 2011), whereas the volume of the mastoid is highly variable. However, the gross anatomy is also dominated by the large numbers of air cells, which lead to an increased surface area such that its area-to-volume ratio (AV ratio) is enhanced. The mastoid size has traditionally been investigated by conventional X-ray projections (Schüller projection), wherein the extent of pneumatization can be measured by planimetry. This measure correlates with the mastoid volume, so that the ratio of volume to planimetric area is 0.7 (Cinamon 2009). In clinical work, Schüller projections are still used by some otosurgeons; they are simple to obtain, yet gives a good impression of the pneumatization.

More detailed analysis has emerged during the last decade based on computed tomography (CT) scans. Park et al. (2000) reported an average surface area for normal adult mastoids to be 167 cm^2, while the average volume was 10.4 cm^3; that is, the AV ratio was 16 cm^{-1}. These findings were supported by Alper et al. (2011). The gas exchange function previously discussed can no doubt be enhanced by the larger surface area if the mucosa is well vascularized. Consequently, it is important to determine both the surface area and volume, and to include the AV ratio in the analysis (Park et al. 2000; Alper et al. 2011). The literature is sparse on diseased ears, but recently Csakanyi et al. (2010) have reported on the mastoid area and volume in children with otitis media with effusion (2–18 years). They have found the AV ratio is higher in diseased ears, which seems unexpected and needs further investigations (Csakanyi et al. 2010).

The histological structure of the mastoid mucosa may also be adapted to gas exchange. According to some authors, the mucosa is relatively thin with an epithelium of flat cells and an underlying loose connective tissue with a rich vascularization (Hentzer 1970; Ars et al. 1997; Takahashi 2001). In comparison with the ME mucosa, the epithelium of the mastoid is lower and the distance from the surface to the underlying capillaries is significantly smaller (Ars et al. 1997). These features also favor gas exchange by a smaller diffusion distance.

5.7.3 Mastoid Passive Pressure Buffering

According to Sadé (1992), the mastoid may function as a passive pressure buffer, so that in a larger mastoid any ME pressure change induced by pressure change in the ear canal will be buffered or absorbed in the ME cleft, whereas in a smaller (non-pneumatized) mastoid this will not be feasible to the same extent. In agreement, smaller non-pneumatized sclerotic mastoids are correlated to retractions and atelectasis of the TM (Sadé 1992; Cinamon and Sadé 2003). This theory, which is based on clinical observations, has been contradicted by experimental research

(Doyle 2000). However, more recent work tried to explore this issue further: Doyle (2007) noted that large mastoid volumes are associated with smaller changes in pressure, which may actually support the notion that the mastoid is indeed a gas reserve. Swarts et al. (2010) concluded that the mastoid may function as a gas reserve only if its perfusion/surface area ratio is much lower than that of the ME itself.

5.7.4 Mastoid Mucosal Perfusion

Whereas ME cleft gas exchange has been held responsible for changes in ME pressure, an alternative hypothesis was proposed by Magnuson (2003). According to him, changes in perfusion may alter the congestion of the mucosa, and hence its thickness, which ultimately affects the ME pressure. A calculation based on the AV ratio reported by Park et al. (2000) shows that a small change in mucosal thickness of only 6 μm can alter the ME pressure by 1 kPa (Magnuson 2003). A similar mechanism has been found in diving mammals adapting to pressures at high depths in water; these animals have rich submucosal cavernous sinuses in their ME mucosa (Stenfors et al. 2001).

5.7.5 Recent Clinical Experiments on Mastoid Regulatory Function

Recent clinical experiments demonstrated that the mastoid can function as an active counter-regulator of small experimental deviations of ME pressures in both negative and positive directions without the involvement of the ET (Gaihede et al 2010). Fig. 5.8 depicts an experiment in which a positive ME pressure was induced by injection of a small amount of air, and the resulting counter-regulation of pressure was measured via the mastoid over 10 min. The counter-regulation was gradual and continued into negative pressures. Similar gradual counter-regulation was found for negative pressures. These responses are independent of the ET and can be related only to the mastoid; they may be explained both by changes in mucosa volume, as well as gas exchange (Gaihede et al. 2010).

At larger pressure deviations the counter-regulation also included openings of the ET, depicted as steeper pressure changes with a step-like pattern. Thus, the overall active regulation may consist of a complementary system including both the mastoid and the ET (Gaihede et al. 2010). Whereas the ET acts intermittently, the mastoid regulation of ME pressure acts continuously, and thus may play an important role in the long-term pressure loading of the TM, which in turn can be related to the pathological changes and clinical problems discussed in the preceding text.

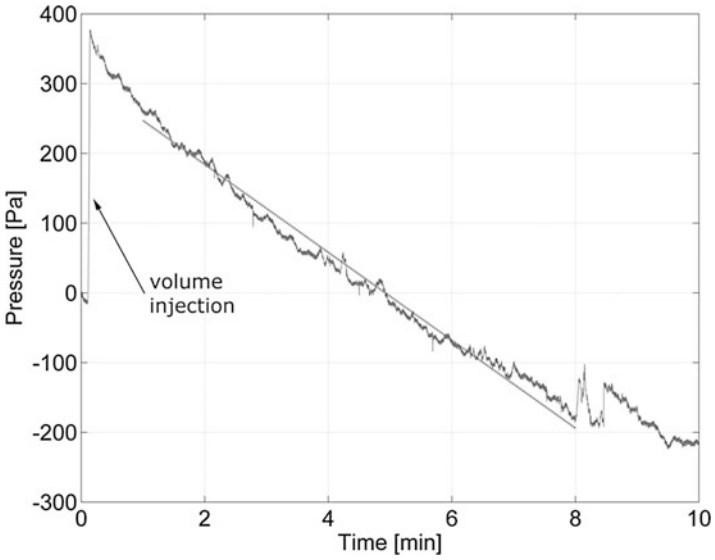

Fig. 5.8 The ME pressure is measured via a catheter inserted into the mastoid tip, and a volume injection of +50 mm^3 of air results in a pressure peak of 378 Pa. The resulting counter-regulation is reflected by a gradual decreasing pressure around − 63 Pa/min. The pressure decrease continues across 0 Pa at around 5 min; at 8 min, a swallow is seen (*M-configuration on curve*), but without any pressure equilibration, that is, no ET opening. After 10 min the pressure is around −200 Pa

5.7.6 Summary and Future Research

The mastoid air cell system has structural properties both in its gross anatomy and histology which favor gas exchange. However, perfusion may also play a role by altering the volume of the mucosa itself, and thus affect the pressure of the ME cleft. Studies on these properties are relatively few and mostly include normal mastoids. Moreover, systematic histological studies of the ME and mastoid mucosa are absent because current data are either sporadic or do not include the entire mastoid but rather the antrum. Such studies should focus on the vascularization of the mucosa. Structural analysis of the mastoid may be improved by applying micro-CT scanning on temporal bone specimens, so that higher resolution may yield more detailed information on volume and surface area.

5.8 Central Neural Feedback Control of ME Pressure

The structure of the mastoid has been described in the previous section. With its numerous air cells and its histological properties it bears many similarities to lung and alveolar structure. Further, in terms of functionality, the overall control of ME pressure regulation may also bear resemblances to the well-known neural feedback control of respiration (Eden 1981).

5.8.1 Basic Studies of Neural Feedback Control

The evidence for a neural feedback control in ME pressure regulation was originally based on experiments in rabbit MEs, in which a neural tracer (horseradish peroxidase) was applied at two sites: (1) the ME mucosa at the promontory around the tympanic plexus and (2) the muscles of the ET and the palate (Eden 1981). For the first site, subsequent labeling of neurons was found in brain stem areas of respiratory control in the nucleus of the solitary tract, whereas for the second site subsequent labeling was found in the brain stem nucleus ambiguous as well as in the trigeminal motor nucleus. In respiratory control, neural projections, from the nucleus of the solitary tract to the nucleus ambiguous and trigenimal motor nucleus, form part of the neural reflex arch, and consequently, a similar reflex arch has been proposed for the aeration of the ME, and thus for ME pressure regulation (Eden 1981).

Based on his observations, Eden proposed that afferent stimulation of the nucleus of the solitary tract is attained by the tympanic nerve (NIX) containing information about ME aeration from oxygen sensitive glomus cells of the tympanic plexus. Further, projections from the nucleus of the solitary tract to the nucleus ambiguous and the trigenimal motor nucleus activate these areas which form the efferent parts by activation of the ET muscles via the trigeminal (NV) and the vagal nerve (NX). Figure 5.1b illustrates the principle and includes additional aspects discussed later.

This hypothesis was considered controversial at the time but has been substantiated in further studies in primates, where similar experiments have shown the same results (Eden and Gannon 1987). Moreover, in important neurophysiologic experiments performed in primates, electrical stimulation of the tympanic nerve resulted in activation of the ET muscles, as recorded by EMG with latencies of 9–28 ms, similarly to other brain stem reflexes (Eden et al. 1990). In addition, the concept of chemoreceptors of the tympanic plexus was extended to include also baroreceptors (Eden et al. 1990).

Similar ideas on reflex control were proposed by Nagai et al. (1989), who demonstrated a decreased ability to equilibrate positive ME pressures by the ET in clinical experiments after anesthetizing the TM by iontophoresis. They also demonstrated modified Vater-Pacinian corpuscles at the periphery of the pars tensa using electron microscopy of the TM, and suggested a mechanoreceptor function (Nagai and Tono 1989). In the same area smooth muscle fibers have been detected, and it has been speculated that these can influence TM tension, but no relation to ME pressure has been demonstrated (Henson and Henson 2000). Rockley and Hawke (1992) reported increasing thresholds of pressure sensation in response to similar TM anesthesia, when they pressurized the ear canal with an experimental tympanometer. In particular, thresholds were significantly increased in patients with TM pathological changes such as atrophy, myringosclerosis, and retractions. Thus, they concluded that an impaired pressure regulation could be attributed to depletion of neural receptors of the TM.

The actual site where receptors needed for ME pressure regulation are situated is unknown. However, due to its higher elastic properties, the pars flaccida of the TM seems to be an obvious position for detection of pressure changes (Hellström and Stenfors 1983). In fact, the pars flaccida contains numerous myelinated and unmyelinated nerve fibers, whereas the pars tensa contains fewer, mostly unmyelinated ones (Lim 1970). Specialized nerve endings serving as mechanoreceptors in the TM were not identified by Lim (1970). However, structures similar to Vater-Pacinian corpuscles were described in the mucosal strands of the ME and the mastoid of normal temporal bones (Lim et al. 1975). In conclusion, stretch-receptors as well as baroreceptors (mechanoreceptors) may be situated in the TM as well as in the ME cleft. The tympanic nerve forms the major part of the tympanic plexus and innervates the mucosa of the ME, the mastoid, and the ET, and thus it seems to be the afferent pathway for any of these receptors (Özveren et al. 2003).

5.8.2 Recent Evidence of Neural Feedback Control

Several more recent studies seem to support the hypothesis discussed in the preceding text. Ceylan et al. (2007) conducted an animal experiment in rabbits, where sectioning of the tympanic nerve was performed. They found that subsequent retraction pockets evolved over 3 months in 48 % of these animals compared to 4 % in controls. In addition, ME effusion evolved in 56 % compared to 12 % in controls. They concluded that tympanic glomus cells, innervated by the tympanic nerve, were involved in ME aeration, and, consequently, disruption of the nerve resulted in atelectasis. Moreover, it seemed that the ET capacity for clearance of mucus had been impaired, as reflected by the frequent effusion found in the study group (Ceylan et al. 2007).

Later, Songu et al. (2009) conducted clinical experiments in which lidocaine was administered: (1) to the promontory in subjects with a dry TM perforation, (2) to the entire ME cavity through a puncture in the TM, and (3) onto the lateral surface of the intact TM. Changes in ET function were subsequently determined using tympanometry, and automated Williams testing reflecting the opening ability of the ET. In groups 1 and 2, the ET function was significantly impaired, whereas in group 3 normal function was demonstrated. Their study compares with the methods applied by Nagai et al. (1989), though they found impaired ET function in cases with an intact TM. However, their anesthesia protocol was more effective, as they used iontophoresis to paralyze any neural activity, which was not employed by Songu et al. (2009). Hence, results reported by Songu et al. (2009) do not exclude the possible role of mechanoreceptors in the TM. The experiments conducted in groups 1 and 2 show that paralyzing the tympanic plexus results in an impaired ET function. Thus, a functional connection between ME afferents and ET efferents has been demonstrated.

Advances in neurophysiologic techniques include measurements of evoked brain potentials from various stimuli and the application of multichannel EEG

recordings. This method includes up to 128 electrodes, where neural activities can be determined in a three-dimensional system, and combined with source localization analysis. Such a technique has been employed in clinical experiments in which evoked brain potentials have been measured in response to static pressure stimulation (3 kPa at 1 Hz) of the TM. Distinct activation of the brain stem was demonstrated with latencies around 5 ms, and with subsequent extension of neural activation to the cerebellum (Sami et al. 2009). Although the exact localization of the brain stem cannot be located to the nucleus of the solitary tract (Eden 1981; Eden and Gannon 1987), in similar control experiments, where acoustic stimulation (white noise) was employed, a separate brain stem activation was found with subsequent extension superiorly into the brain. Subsequent activation of the cerebellum was not possible to demonstrate using previous neural tracer techniques, as these tracers do not extend to second-order neurons (Eden 1981; Eden and Gannon 1987). However, in view of the static pressure experiments, this activation most likely relates to cerebellar nuclei (the fastigial nucleus). This nucleus shows connections to the trigenimal motor nucleus of the brain stem, which relates to activation of the m. tensor veli palatini involved in openings of the ET (Hecht et al. 1993).

Further evidence from the same experiments has been achieved by wavelet analysis, which describes the frequency contents of neural activity. Because the frequency content of different neural systems usually displays distinct characteristics, wavelet analysis can be used to distinguish between them (Darvishi and Al-Ani 2007). Static pressure stimulation of the TM has resulted mainly in θ-band activity (0–4 Hz), while acoustic pressure stimulation results in α-band activity (7–10 Hz). Thus, more distinct neural activation patterns exist for static and acoustic stimulation of the TM. This supports the idea that separate afferent pathways are related to static pressure stimulation (Gaihede et al. 2008; Sami et al. 2009).

Cortical activation in normal humans was recently demonstrated in a functional magnetic resonance imaging (fMRI) study in response to alternate static pressure stimulation of the TM up to 40 daPa (Job et al. 2011). The activation included the postcentral gyrus in Brodmann area 43, which is also involved in pharyngeal activities. Hence, it might represent a link between the ME and the ET activation (Job et al. 2011).

5.8.3 Summary and Future Research

In summary, various clinical, histological, and physiological experiments, as well as fMRI studies, have been employed in search for an overall mechanism of ME pressure regulation. This mechanism seems as obvious as respiratory control, and accordingly it would constitute a continuous process; thus, monitoring MEP directly with an intact TM over longer periods of time seems very important to understand its temporal variation and development of abnormal regulation

(Gaihede et al. 2010). The experiments performed by Eden and Gannon (1987) are important because they linked stimulation of the tympanic nerve directly to ET muscular activity. However, proper stimulation by static pressures seems a prerequisite to confirm the hypothesis, and improved experiments in this line will be valuable.

The role of the peripheral receptors is also important. In the study performed by Rockley and Hawke (1992) subjects were unable to distinguish positive from negative ear canal pressures. Hence, it may be hypothesized that pressure sensation depends on (1) highly sensitive stretch-receptors related to the highly flexible pars flaccida or less probably the pars tensa of the TM; these receptors may not be able to detect direction of pressure and (2) direction-sensitive baroreceptors in the ME cavity and the mastoid. Further research is needed to describe the locations and functions of such receptor components.

The studies reviewed in this section all focus on the role that the ET plays in pressure regulation, while the possible role of the ME and the mastoid mucosa is not mentioned at all. Whether perfusion of the ME and mastoid is involved still remains uncertain, but in principle this may be accomplished by vascular reflexes (Fig. 5.1b). These may constitute efferent autonomic innervation of precapillary arterioles of the mucosa or by local neurotransmitters. It constitutes a separate challenge for future research to demonstrate any link between static pressure changes and the mucosal perfusion.

5.9 Summary

In normal circumstances, the ET is closed and the ME cleft forms a closed gas volume. Because the volume is closed, pressure differences between the ME and the ambient pressures can easily develop on time scales from fractions of seconds to many hours. When such a pressure difference is present, the TM is subject to a mechanical load. If the load is large, it affects hearing ability, but even small pressure loads may have an effect on the TM in the long run. Long-term pressure loads on the TM are involved in the formation of a series of clinical ME conditions, which include otitis media with effusion, retraction, atelectasis, and cholesteatomas. These conditions can lead to degeneration of ME structures and to decreased hearing.

The balance between ME pressure and ambient pressure can be maintained either by changing the amount of gas in the ME cavity, or by changing ME volume. The only ways the volume of the cavity can change is by displacement of the TM, by changes in the congestion of the mucosa, or by fluid secretions. In older literature, it was suggested that the pars flaccida has an important pressure regulative function, but more recent quantitative measurements have shown that this pressure regulative role is marginal. Still, it may be important in buffering very small, rapid pressure changes. Displacement of the entire TM can reduce pressure changes in the order of 20–70 %, depending on the total volume of the ME cleft. Pressure compensation is much larger in a small ME cleft as opposed to a large one.

This finding may be important in the management of ears that show clinical problems related to impaired pressure regulation. Changes in thickness of mucosa also can alter the ME cleft volume. Such changes can happen over long time periods, for instance in case of inflammation, but changes in blood perfusion can in principle alter the mucosa thickness on a short time scale.

Gas can enter or leave the ME cavity in two ways: through the ET or by gas exchange. During actions of swallowing, the ET transfers very small amounts of gas from the nasopharynx to the ME or vice versa. When very large pressure differences between the ME and the nasopharynx develop, perhaps due to a sudden change in ambient pressure, the ET opens spontaneously to equilibrate the difference. Thus, the ET plays a role in pressure regulation, and much research has focused on this aspect. Hitherto, ET function tests do not correlate well with clinical problems; thus the behavior of the ET alone cannot be used to explain them. One possible explanation lies in the additional role of the mastoid, which has recently attracted much interest among researchers.

Gas exchange is an important factor in ME pressure regulation. When there is an imbalance between the partial pressure of the gas in the ME, and its partial pressure in the blood, it will enter or leave the ME cleft through the mucosa. Experiments have shown that this exchange process can go rather fast, and that significant amounts of gas can leave or enter the ME in this way. Whether the gas exchange process of each gas is limited mainly by diffusion or by perfusion is still a point of debate, but it is a debate of high relevance: if the process is limited by the diffusion through the ME mucosa, the gas exchange rate cannot change very quickly. If, however, blood perfusion of the mucosa is the main limiting factor, quick changes in perfusion rate can alter the gas exchange rate on a short time scale. If this is the case, gas exchange could form an essential part in an active pressure regulation mechanism. Experimental evidence indicates that at least CO_2 exchange is limited by perfusion.

Recent results indicate that the overall regulation of ME pressure includes an active neural feedback control based on peripheral mechano-receptors, and, mainly, respiratory brain stem centers. These centers may control the ET activity and also perfusion properties of the ME cleft. If such neural control exists, further research will bring insights into its connection with impaired ME pressure regulation. This may open up entirely new directions for treatment. Differences between ME pressure and ambient pressure are an essential part of everyday life. New insights in ME pressure regulation include future experiments on gas exchange, TM and ME biomechanics, the action of the ET and the mastoid, as well as any neural components. Because there is a clear connection between impaired ME pressure regulation and pathology, ongoing and future fundamental research is very important, as several questions still remain unanswered. This work will bring better insight into the underlying mechanisms, so that the development of pathologic changes can be prevented and treatment strategies improved.

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