Eustachian tube pressure equilibration. Temporal analysis of pressure changes based on direct physiological recordings with an intact tympanic membrane

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1. Introduction

The Eustachian tube (ET) plays an important role in pressure regulation of the middle ear (ME). In a clinical context the significance of underpressures in the ME are well known being related to both otitis media with effusion and a series of sequelae to chronic otitis media (Bluestone, 2004). Basically, these underpressures are explained by a net gas absorption of air from the ME cavity including the mastoid which is insufficiently counter-balanced by a decreased air supply due to an impaired ET function (Doyle, 2000).

The overall regulation of the ME pressure has previously been explained by a neural feedback reflex mechanism, where mechanoreceptors in the tympanic membrane (TM) and/or the ME cavity formafferent information to respiratory brain stem centers, which subsequently results in efferent activation of the muscles responsible for the opening of the ET (Eden et al., 1990). This hypothesis has been supported by a series of subsequent studies, and in its context an intact tympanic membrane (TM) is critical for a physiological afferent response to any pressure alterations (Gaihede et al., 2008). Moreover, the opening of the ET is elicited as a neural reflex,
which would be expected to express an individual though rather constant duration.

The efficacy of the pressure equilibration of an ET opening can be described by the magnitude of the pressure change during an opening. From a physical point of view this depends on the pressure difference between the ME and the ambient pressure, i.e. the pressure gradient, so that the gradient drives the equilibration. However, the duration of the ET opening may in theory also play a role, since a higher gradient may influence the afferent neural input to the brain stem (Sami et al., 2009). Thus, the subsequent effefficient activation of the ET opening reflex may become of longer duration in order to efficiently equilibrate for higher gradients. It follows that in order to investigate these aspects of the ET physiology an intact TM has to be preserved to maintain an intact reflex mechanism.

Investigations of the ET function with an intact TM are very few. Previously Elner et al. (1971) has reported on experiments in a pressure chamber, but the recordings did not describe the opening time of the ET. More recent methods include sonotubometry applied in clinical investigations of the ET function; however, this approach does not allow determination of the ME pressure (Mondain et al., 1997; Asenov et al., 2010). Similarly, detailed video endoscopic recordings have been employed in the analysis of ET function, but also lack information about the pressure changes described previously (Jacobsen et al., 2007; Gaihede et al., 2010).

Recently, short term regulation of experimental changes in ME pressure has been described, where the ME pressure has been measured directly through the mastoid; hence the TM remained intact during the experiments (Gaihede et al., 2010). In these investigations we have demonstrated a complementary pattern of pressure equilibrations in terms of the magnitude of pressure change during an ET opening to be determined; these data showed a more equal mixture of both patterns. In this study we aimed to investigate these aspects of the ET physiology and inc-

2. Method and materials

2.1. Subjects and surgical procedure

Twelve subjects referred to parotidectomy volunteered for the experiments. All participants had normal ears, which included a negative history of ME disorders, normal otomicroscopy, and normal pure tone audiometry as well as tympanometry. Informed and written consent was obtained from all subjects and the experiments had been approved by our Ethical Committee (2005/50).

At the end of the parotidectomy procedure, where the lateral tip of the mastoid had been routinely exposed, a small hole (3 mm) was drilled at its surface extending into the superficial air cells of the mastoid (0.5–1.0 cm). A sterile suction catheter (diameter 3.5 mm) was tightly inserted into an air cell and connected to a pressure transducer. The catheter was left in the wound similarly to a traditional wound drainage tube and routine suturing of the connective and cutaneous tissues secured the position and tight-

2.2. Instrumentation

The pressure transducer (small brass cylinder 9 × 30 mm) was connected to a sampling unit contained in a small box (28 × 65 × 138 mm), which was carried by the subject in a breast pocket of their shirts and secured by a safety pin. The transducer was set to a range of ±400.0 (±0.1) daPa. The sampling unit monitored and stored pressure data continuously at 10 Hz. Data recording and processing was performed by a Matlab graphical user interface. Details on the procedure and instrumentation have been described previously (Jacobsen et al., 2007; Gaihede et al., 2010).

2.3. Experiments

The experiments were performed in the morning on the day after surgery and consisted of on-line recordings of the counter-regulation after experimentally induced alterations in ME pressure. These alterations were induced by inserting a metal three-way stop-cock to a cut in the catheter between the mastoid and the transducer and connecting a 500 μl gas syringe. Thus, six separate experiments were performed at volume deviations of ±50, 100, and 200 μl, respectively, which produced a variety of over- and underpressures. The resulting counter-regulation was studied and recorded over shorter time frames of 10 min. The subjects were placed in a comfortable chair to relax and were allowed to read; we did not direct attention to swallowing, but only observed the subject and the pressure changes on the monitor.

2.4. Data analysis

The overall counter-regulation of the pressure changes described two basic patterns: 1) a gradual response displaying a smooth decrease or increase in pressure, and 2) step-wise response described by a small series of steeper changes toward baseline at 0 daPa (Fig. 1). The individual subjects showed different overall patterns, so that some presented predominantly gradual responses, others presented predominantly step-wise responses, while others showed a more equal mixture of both patterns. In this study we focused on the step-wise response of pressure changes, since these were related to ET openings; in order to provide a sufficient number of observations, only subjects with a total of ≥10 ET openings during the total set of six experiments were included for the subsequent analysis.

The separate ET openings were characterized by a set of variables illustrated in Fig. 2. The pressure gradient described the difference between the actual pressure and the base-line or ambient pressure; the pressure change described the difference between the actual pressure and the subsequent pressure after the ET opening (ΔP); and the ET opening time described the duration of the opening (Δt).

Based on the pressure change and the ET opening time, the rate of pressure change could be also estimated (ΔP/Δt). In order to exclude smaller incidental pressure fluctuations from being analyzed as ET openings, only events with a pressure change >3.5 daPa and an opening time <1.5 s were defined as ET openings.

2.5. Statistical analysis

Basic descriptive statistics was applied to characterize the data, whereas correlation, linear regression and multiple linear regression analysis were applied to describe any correlations between the variables; a p-value <0.05 was considered significant.
Fig. 1. A series of three of ET openings with step-wise counter-regulation in response to an experimental overpressure (Subject 4: injection of 50 μl of air). The 1st ET opening appears at 30 s. After additional two openings the pressure has equilibrated to almost 0 daPa at time <110 s (Reproduced with permission from Wolters Kluwer Health; Gaihede et al., 2010).

**3. Results**

**3.1. Basis measures**

From the group of 12 subjects participating in this study, one subject was initially excluded due to a very sclerotic mastoid, which complicated a safe drilling without posing risks to the facial nerve (Subject 6); another two subjects were subsequently excluded due to leakage of the catheter into the wound (Subjects 1 and 12). From the remaining group, four subjects showed a set of ≥10 ET openings, whereas five subjects predominantly showed gradual responses and few ET openings (<10). The latter group only differed by their smaller numbers of ET openings; their courses of experiments and especially their patterns of pressure equilibrations were otherwise identical to the group with ≥10 ET.

These four subjects displayed individually different ranges of pressure gradients in response to the volume deviations; their ranges have been depicted in Table 1. Similarly, the pressure changes resulting from the ET openings showed considerable range of pressures with an overall mean of pressure equilibration capacity of 30 daPa; their distributions including their ranges appear in Table 1. The distribution of the ET opening times only showed minor variation with an overall mean of 0.34 s; the distributions have been outlined in Table 1. Finally, the distribution of the pressure change rates estimated by ΔP/Δt appears in Table 1.

**3.2. Correlations**

In Fig. 3 the overall correlation between the pressure change and the pressure gradient has been illustrated presenting a significant positive correlation (Table 2: p < 0.001). Thus, for larger pressure gradients, larger pressure equilibrations can be expected. The individual sets of data all showed similarly significant correlations; however the slopes displayed some variations (Table 2).

In Fig. 4 the overall correlation between the pressure change and the ET opening time has been depicted; this relationship did not show any significant correlation (Table 3: p = 0.34). Similar results were consistently found for the individual data sets (Table 3). Thus, the pressure change was not related to the opening time.

In Fig. 5 the overall correlation between the ET opening time and the pressure gradient has been shown; this relationship similarly did not show any significant correlation (Table 4: p = 0.16). Similar findings were consistently demonstrated for the individual data sets (Table 4). This meant that a larger pressure gradient did not influence the ET opening time.

Multiple linear regression analysis was applied to investigate the overall relationship between the pressure change and the independent variables pressure gradient and ET opening time; this analysis revealed a significant correlation with the pressure gradient (p < 0.001), whereas the correlation with the ET opening time was not significant (p = 0.56; r² = 0.77; N = 75).

**Table 1**

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>Pressure gradient range (daPa)</th>
<th>ME ΔP ± SD ΔP</th>
<th>Mean Δt ± SD (s)</th>
<th>ME ΔP/Δt ± SD (daPa/s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>34 ≥ 105 to 64</td>
<td>0.36 ± 0.16</td>
<td>34 ± 28</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>11 ≥ 32 to 35</td>
<td>0.40 ± 0.13</td>
<td>27 ± 20</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>10 ≥ 35 to 390</td>
<td>0.46 ± 0.23</td>
<td>292 ± 181</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>20 ≥ 199 to 183</td>
<td>0.23 ± 0.15</td>
<td>144 ± 102</td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>75 ≥ 325 to 390</td>
<td>0.34 ± 0.18</td>
<td>97 ± 124</td>
<td></td>
</tr>
</tbody>
</table>

* For the gradient, ΔP and ΔP/Δt the distributions have been determined from their numerical values. SD = standard deviations; n = number of observed ETOs.
The pressure change rate demonstrated an overall significant positive correlation to both the pressure gradient (Fig. 6) and the pressure change (Fig. 7) (Tables 5 and 6; \( p < 0.001 \)). The analysis of the individual data sets demonstrated results consistent to the overall analysis (Tables 5 and 6). The pressure change rate was not related to the ET opening time (Fig. 8 and Table 7).

4. Discussion

The present experiments reflected pressure equilibrations by ET openings in response to experimental pressure changes in ME. Since these measurements were performed directly via the mastoid, the TM was kept intact, and the ET openings may be considered physiological reflex openings. Further, the pressure and time resolution was high, so that the individual ET openings could be described in details, and the relevant parameters determined. The analysis of these parameters showed that the pressure change during an ET opening was significantly correlated to the actual pressure gradient which confirms that the gradient drives the pressure change (Fig. 3; Table 2). Basically, this is also reflected by the stepwise decreasing pattern of equilibrations illustrated in Fig. 1. In contrast, the ET opening time showed only minor variation (Table 1) and the pressure change did not correlate to the opening time (Fig. 4; Table 3); moreover, the opening time did not correlate to the pressure gradient (Fig. 5; Table 4). Combined analysis by multiple linear regression confirmed these findings that the efficacy or magnitude of the pressure changes was significantly correlated to the gradient (\( p < 0.001 \)), but not to the opening time (\( p = 0.56 \)).

Table 2

Linear regression and correlation analysis of the pressure change versus the pressure gradient for individual subjects and overall ETG’s observed (Fig. 3).

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>( N )</th>
<th>Slope</th>
<th>( r^2 )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>34</td>
<td>0.30</td>
<td>0.61</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>0.60</td>
<td>0.93</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>0.80</td>
<td>0.98</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>0.24</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overall</td>
<td>75</td>
<td>0.57</td>
<td>0.77</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

In conclusion, pressure changes during the ET openings were not affected by changes in the opening time, but only correlated to the pressure gradient. Moreover, the opening time was not influenced by the pressure gradient. Thus, larger pressure gradients are not equilibrated to ambient pressure by longer ET opening times, but rather a series of ET openings similar to the pattern illustrated in Fig. 1; a similar illustration has been shown by Elner et al. (1971).

The mean opening time was 0.34 s (Table 1); in accordance, sonotubometric studies in normal ears by Mondain et al. (1987) reported a mean opening of 0.43 s, whereas Asenov et al. (2010) found a mean of 0.36 s. More recently, Poe and Pyykkö (2011) reported a mean cycle time of ET opening of 0.995 s, but this included the full duration of the muscular activity observed, which may well exceed the actual opening time.

The rate of pressure change was estimated by the pressure change divided by the opening time (\( AP/\Delta t \)), and the mean rate was 34 daPa/s ranging between –147 and 73 daPa/s (Table 1). However, the rate of pressure change will be an exponential function, so that our calculations here strictly reflected only an estimate; we have not found any studies in the literature reporting on this measure. The rate of pressure change correlated significantly to both the pressure gradient (Fig. 6; Table 5) as well as the pressure change itself (Fig. 7; Table 6). This only confirms that for higher pressure gradients and for higher pressure changes, a faster pressure equilibration can be expected. Based on the previous correlation analysis of the ET opening time, the rate of pressure change expectedly did not correlate to the opening time (Fig. 8; Table 7). This can be explained by the relative constant duration characterizing the ET opening time for individual subjects and overall ETG’s observed (Fig. 4).

Table 3

Linear regression and correlation analysis of the pressure change versus the ET opening time for individual subjects and overall ETG’s observed (Fig. 4).

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>( N )</th>
<th>Slope</th>
<th>( r^2 )</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>34</td>
<td>–5.02</td>
<td>0.00</td>
<td>0.72</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>31.22</td>
<td>0.14</td>
<td>0.26</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>145.89</td>
<td>0.04</td>
<td>0.56</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>25.62</td>
<td>0.01</td>
<td>0.61</td>
</tr>
<tr>
<td>Overall</td>
<td>75</td>
<td>36.46</td>
<td>0.01</td>
<td>0.34</td>
</tr>
</tbody>
</table>
openings. We have not found any studies reporting on the rate of pressure changes in ET openings.

Our subjects were continuously observed along with the monitoring of the pressure. The ET openings revealed very clearly as the step-wise changes in pressure illustrated in Figs. 1 and 2; in the majority of cases swallowing could be observed. However, in some cases, where doubt was present, the subject was asked, and usually confirmed a swallow. Thus, ET openings seemed always related to a swallow, whereas swallow can be seen without an ET opening (Mondain et al., 1997; Gaihede et al., 2010). Thus, the situation in these experiments reflected to high degree physiological circumstances, since openings were mostly unconscious reflecting a response to the experimental changes in the ME pressure. Passive openings of the ET at high positive pressures were not seen in the current experiments, but they could easily be identified at the pressure–time plot; passive openings appear immediately related to the experimental pressure changes. This means that they do not show any pressure plateau between the experimental pressure changes and the pressure equilibration; for instance, in Fig. 1 there is a period of 20 s with a stable pressure around 34 daPa before the first ET opening.

The magnitude of the pressure gradients ranged overall between −325 and 390 daPa (Table 1), and reflected a range of physiological values without causing any discomfort (Gaihede et al., 2010). Correspondingly, the resulting pressure changes during the ET openings also showed wide variation between −213 and 312 daPa reflecting both the variation in pressure gradients as well as individual variations (Table 1). The slopes of the regression lines between pressure change and gradient (Table 2) similarly showed individual variation; these slopes expressed a measure of the individual resistance of the ET, which may be related to the physical parameters of the tube; this measure has not been reported earlier. We did not find any differences between equilibrations of positive and negative pressures based on individual plots of correlations; this is in accordance with the observation that equilibrations are driven only by the physical conditions related to the pressure gradient.

The current experimental approach is limited by experiments in only four normal cases from the group of 12 participants; this was

Table 4
Linear regression and correlation analysis of the ET opening time versus the pressure gradient for individual subjects and overall ET openings (Fig. 5).

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>N</th>
<th>Slope</th>
<th>r²/r</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>34</td>
<td>0.00</td>
<td>0.01/0.08</td>
<td>0.66</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>0.00</td>
<td>0.24/0.49</td>
<td>0.12</td>
</tr>
<tr>
<td>7</td>
<td>10</td>
<td>0.00</td>
<td>0.06/0.25</td>
<td>0.49</td>
</tr>
<tr>
<td>9</td>
<td>20</td>
<td>0.00</td>
<td>0.03/0.17</td>
<td>0.49</td>
</tr>
<tr>
<td>Overall</td>
<td>75</td>
<td>0.00</td>
<td>0.03/0.16</td>
<td>0.16</td>
</tr>
</tbody>
</table>

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explained by the exclusion of the five subjects with relative few ET openings, and the three subjects with technical problems. Moreover, the method included considerable resources related to the recruitment of the participants and their enduring task of coping with the actual experiments for 2½ hours on the day after surgery as well as the additional time needed for surgery and planning in a surgical unit. Altogether, larger scale experiments will be difficult to pursue for these reasons. However, when the instrument functioned properly, it showed a high accuracy and the current set of four ET experiments reflected very reliable measurements. Further, the method is limited by the fact, that it is not applicable to diseased ears, where sclerotic mastoids can be expected (Gaihede et al., 2010). The procedure included drilling a small hole in the mastoid surface and insertion of the catheter which in theory may cause a trauma affecting the results. This methodological intervention is inevitable, but the hole was less than 5 mm deep and 3 mm in diameter. Thus, it affected only a very small part of the mastoid which may be considered insignificant. It should be noted that pressure changes within the mastoid are practically immediately transferred to the ME cavity itself, so that no noticeable damping of the pressure changes occurs (Felding et al., 2003).

Direct recordings of the ME pressure with high sampling rates have also been reported by Tideholm et al. (1996), but they focused on monitoring long-term changes in pressure, as well as they did not maintain an intact TM, but relied on a TM perforation or a ventilation tube to measure the ME pressure. Later Brattmo et al. (2003) using the same method investigated the ET function, but they have only reported on categories of ET function related to the numbers of equilibrations by conscious swallowing in order to reach baseline pressure after experimental pressure changes (Elmer et al., 1971). Thus, despite high accuracy and direct pressure recordings their results are not comparable with the current results.

Various other methods for analysis of the ET function include studies on ET opening pressures (Bunne et al., 2000), sonotubometric studies (Mondain et al., 1997; Asenov et al., 2010), forced response test including inflation/deflation tests (Swarts et al., 2011) as well as video endoscopic studies (Poe et al., 2000); all these methods present limitations due to unphysiological test conditions, but they can be applied in clinical studies investigating larger groups of both normal and diseased ears. This cannot be obtained by the current methodological approach; its value is an accurate set of new physiological data that can be used in modeling of the normal ET function (Sheer et al., 2012). Moreover, our data may be used to characterize ET openings and form the basis for mathematical pattern recognition, which can be used for an automated analysis of larger amount of data recorded from 24- or 48-h monitoring of the ME pressure (Tideholm et al., 1996; Jacobsen et al., 2007).

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