

SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PhD)

Middle ear gas pressure regulation

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The Examination takes place at the Library of the Department of Anatomy, Histology and Embryology, Faculty of Medicine, University of Debrecen at 11.00 a.m. 16th May, 2014

Head of the **Defense Committee:** Prof. Miklós Antal MD, DSc
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The PhD Defense takes place at the Lecture Hall of Bldg. A, Department of Internal Medicine, Faculty of Medicine, University of Debrecen at 1.00 p.m. 16th May, 2014

1. Introduction

Gas pressure balance ensures that the middle ear (ME) pressure is similar to that of the atmosphere. This is crucial to the physiological function of the ME. Imbalances in gas pressure may lead to acute or chronic inflammation of the ME. The gas volume of the ME is maintained primarily by gas exchange with the nasopharynx and the mucosal blood vessels of the ME. Gas pressure of venous blood is lower than the ME and atmospheric pressure. This difference results in gas exchange between the ME and the mucosal blood vessels. This results in a pressure decrease in the ME, which is compensated with atmospheric air during the periodic Eustachian tube (ET) opening. This cycle is repeated nearly a thousand times per day at normal ME function.

Otitis media with effusion (OME) is the most common cause of acquired conductive hearing loss in childhood. Importance of the disease is explained by its high incidence, variability in symptom severities and clinical course, as well as its potential negative impact on psychosocial development and social integration at a later age. There are no exact statistics on OME incidence in Hungary. 2.2 million people are diagnosed with OME in the USA each year. The direct and indirect healthcare costs are estimated to be around 4 billion dollars there [Shekelle, 2003]. This reflects the health and social impact of OME.

Around 90% of children exhibit symptoms of OME for some period of time before school age [Tos 1984]. This is most prevalent between six months and four years of age, which coincides with the definitive period of speech development. Accumulation of effusion in the ME usually ceases after three months. However, it re-occurs in 30-40% of cases and lasts over a year for 5-10%. Prevalence of the disease decreases after six years of age.

ET dysfunction is determining in the development of OME. However, pathophysiology of the disease is not entirely clarified. Spontaneous recovery, recurrence and prolonged clinical course are equally characteristic to the disease. In 5-30% of persistent OME cases may develop segmental atrophy, atelectasis, ossicular chain disruption, TM perforation, tympanosclerosis, otorrhoea or cholesteatoma. Therapy aims to normalize hearing and prevent permanent impairment of the ME. For persistent cases, international treatment guidelines primarily recommend adenoidectomy and myringotomy,

or adenoidectomy and ventilation tube. However, these methods have only been proven to be effective on the short term. This fact explains the wide individual variety of therapeutic approaches in OME between countries and institutions. The prevention and effective long-term clinical management of OME remain to be addressed by pediatric otology.

2. History

The ME is a complex system including the ET, the tympanic cavity (TC) and the MCS, which varies in extent for each individual. In healthy adults the MCS is well developed. According to clinical findings, the mastoid pneumatization is decreased in chronic otitis media, cholesteatoma, and OME. Genetic and environmental etiologic factors have been considered, but these remained controversial. The mastoid pneumatization has been examined by planimetric and volumetric measurement methods. The volume of interconnected air cells is difficult to measure directly. *Diamant's* planimetric method was fundamental in standardizing the measurement of the mastoid size by applying 2-dimensional radiographs. It is a reliable method to compare patients of similar age, although it is not suitable for measuring the actual volume or surface area of the MCS. *Todd et al* found a relatively weak correlation between computed tomographic and various radiographic methods after examination of 30 adult pyramidal bones ($r=0.57-0.74$). Computed tomographic scanning seems superior over other imaging methods in establishing mastoid pneumatization. A plethora of reports on planimetric mastoid size in healthy children and children experiencing OME can be found in the literature. Three-dimensional determinations are, however, missing. *Lee et al* reported only some mastoid volume data from healthy children aged 0 to 19 years. Several studies determined the volume of adult MCS. Less attention was paid to mastoid surface area measurement. This is an important parameter of the middle ear gas exchange through the mucosal lining. No data are available in children for the MCS surface and volume in relation to the development of OME.

The physiological role of the MCS has not yet been entirely clarified. Certainly, the MCS buffers the environmental and ME pressure changes proportionately to its volume. Its morphology and histological structure

suggests that gas exchange takes place between the ME and the surrounding mucosal blood vessels. The surface area of the mucosal lining is one of the determining factors of gas exchange in the ME. *Park* was the first who published data on the extent of the ME surface area based on 3D CT scans of normal adults. He noted that the well-pneumatized MCS has an extensive surface area that is proportional to the volume. Histological studies indicate that the postero-superior part of the ME (epitympanum, aditus ad antrum, antrum mastoideum and the MCS) is the primary place of gas exchange whereas the antero-inferior part (meso-, hypotympanum and the ET) mainly serves for mucociliary clearance function.

Gas pressure balance ensures that the ME gas pressure is nearly equal to atmospheric pressure, which is a prerequisite of an inflammation free ME, and normal hearing. The MCS volume, the mucosal surface area, and the ET play a crucial role in this precisely regulated complex process. Still less is known about the details of it. The ME is a closed system. In vivo examination of the ME gas pressure regulation is difficult. Data of the animal experiments cannot be directly adapted to the human ME. Mathematical and computer modeling provides a significant progress in this field. It is highly effective in analyzing the potential influencing factors of the ME function and their interactions, as well as the processes contributing to ME pathology. However, validation of mathematical descriptions is crucial in the modeling. The first compartmental mathematical models to describe ME gas exchange were developed by *Doyle et al* [1999, 2000]. *Fink and Ar* [2003] have had an important role in further developing the model of ME gas exchange. The results of their mathematical models were consistent with human experimental data. Therefore, the mathematical descriptions and diffusion constants calculated by them serve as appropriate basis for further research.

At closed ET, differences in the partial gas pressures (mainly N_2 , O_2 , CO_2) between the air of the ME and blood result in gas exchange through the mucosal lining of the MCS and the epitympanum. As a consequence, the ME total pressure (METP) decreases. According to the General Gas Law, the rate of the gas flow during passive gas exchange is directly proportional to the extent of surface area. The rate of the pressure decrease due to gas exchange is a function of the surface area-to-volume ratio in the ME. When

the ET opens, air flows through it and the METP is balanced. The tympanic membrane (TM) acts as an active pressure buffer in the maintenance of steady state condition. It compensates for small, sudden pressure changes. Mathematical descriptions of *Doyle* support that the effective pressure buffering function does not require too large ME volume. Furthermore, his calculations indicate that the MCS has a capacity of limiting the rate of transmucosal gas exchange, and consequently the METP change, depending on its volume. The latter suggests that the ME surface area-to-volume ratio is a function of the ME volume. However, calculations could not support by clinical data so far. We have not found any evidence of mathematical/computer modeling in the literature simultaneously considering ME gas pressure balance in relation to normal and pathological ET function. In some chronic OME cases, segmental atrophy of the TM, atelectasis and cholesteatoma formation can occur, causing mild to moderate conductive hearing loss. In atelectatic ears and cholesteatoma cases restoration of normal ME function and hearing while maintaining successful long-term surgical outcome remains a challenge in the field of otomicrosurgery. Mastoid obliteration, which has recently become a frequently applied procedure, has been proved effective to decrease recurrence rate and to improve long-term outcome in cases of cholesteatoma. The surgery consists of one-stage eradication of cholesteatoma, applying canal wall down mastoidectomy and total reconstruction procedure, obliterating the mastoid cavity and epitympanum (commonly using bone pat ), canal wall reconstruction, and ossiculoplasty. Obliteration technique results in an ~0.6 ml aerated ME volume and a smaller, shallower cavity. The long-term surgical effectiveness of the technique is supported by the proper eradication of the cholesteatoma as well as stabilization of the ME gas pressure balance. However, the physiological basis of the gas pressure normalization is currently unknown.

3. Aims of the thesis

This study focuses on a better understanding of the healthy and pathological ME function. Potential role of the ME anatomical (volume, surface, surface area/volume ratio) and physiological (gas exchange, gas pressure balance) changes in the development of OME and its sequelae (retraction pocket, atelectasis, cholesteatoma) was examined. Determinant factors in the development of chronic OME were analyzed. To improve the long-term effectiveness of cholesteatoma surgery, contribution of mastoid obliteration technique to the ME gas pressure balance stabilization was investigated.

1. Characteristics of healthy and pathological ME pneumatization in healthy children between the ages of 2 and 18 years and age matched children with OME were examined.
2. Applying a mathematical model, ME pressure changes were predicted in different ME volumes considering normal and pathological ET function.
3. Development of ME gas pressure balance following mastoid obliteration was evaluated.
4. Change in ME pneumatization (volume, surface and surface-to-volume ratio) in cases of persistent OME after five years was assessed.

4. Patients and Methods

4.1 Comparative examination of the ME pneumatization in healthy children aged 2-18 years, and age matched children with chronic OME

Computed tomographic scans of 96 children between the ages of 2 and 18 years (46 girls and 50 boys) were analyzed. Forty children (24 girls and 16 boys) without otological history served as healthy control group (74 ears) in the age range of 2.5 to 17.5 years (mean age \pm SD: 8.51 \pm 4.2 years). Computed tomographic examination of these children was indicated by head trauma or suspicion of intracranial space-occupying process. Negative middle ear history means no otitis media in the previous 3 months and fewer than 3 acute purulent otitis media episodes overall. Other inclusion criteria were negative otoscopic findings and A- or C1-type (3 ears) tympanogram. Fifty-six children (22 girls and 34 boys) from the OME group (108 ears) after adenoidectomy were in the age range of 2 to 17 years (mean age \pm SD: 7.1 \pm 3.2 years). They were reviewed regularly during the last one year because of OME and have had one or more ventilation tube insertion procedures in their history. Further inclusion criteria were TM retraction, presence of middle ear effusion, limited movement of the TM by pneumatic otoscopy, and B- or C2-type tympanogram. The age distribution of the two study groups did not differ significantly from each other ($p = 0.0982$). Sex distribution in the OME group shows a higher prevalence among boys (61%). Computed tomographic examinations of the traumatologic and neurologic patients were done using the conventional technique (normal dose, orbitomeatal plane). Ears exhibiting pyramidal bone fracture and consecutive hematotympanon were excluded from the study. Computed tomographic examinations were performed by a computed tomographic scanner (Light-Speed Ultra CT; General Electrics, Waukesha, WI, USA) after obtaining informed parental consent. The images of children with OME were obtained with a special low dose (120 kV, 100 mA) in axial plane to assess the potential mastoid process. Images were converted into DICOM (Digital Imaging and Communication in Medicine) file and processed by a custom-developed software. Standardized parameters of the data were saved in a CD (slice thickness, 1.25 mm; matrix, 512 X 512; and vertebra algorithm). To

determine the air content of the ME, values between the lower thresholds of -1024 Hounsfield unit (HU), corresponding to air, and an upper threshold of -200 HU (mucus, soft tissue) were used. Comparative measurements of the bony ME structure were conducted applying -1024 HU as the score for lowest threshold (air) and +200 HU as the upper threshold (trabecular bone). This disregards mucus or soft tissue content and mucosal lining, thus slightly overestimating the actual volume and surface area of the MCS. This setting proved to be adequate for comparing the dimensions of MCS in healthy and OME children. Outlining the extension of the MCS slice by slice, the 3-dimensional (3-D) reconstruction and the surface and volume determinations were automatically performed by the software.

The tympanic cavity, antrum, periantral, central mastoideal, tegmental, sinodural, perisinous, perifacial, apical, zygomatic, and perilyabyrinthine regions were considered. Statistical analyses were performed using SPSS software (SPSS, Inc., Chicago, IL, U.S.A.). The mean mastoid surface area and volume values and SDs for each age group in healthy and OME children have been calculated. Correlations between left and right MCS were determined. The Mann-Whitney test was used to compare the means of surface area and volume values of the healthy and OME groups and the intractable OME group. Intractable OME was characterized by structural changes of the TM, moderate conductive hearing loss, and more than one ventilation tube insertion. Statistically significant differences were considered at $p < 0.05$.

4.2 Mathematical model predictions of ME gas pressure balance in normal and pathological conditions

Model description: Mathematical calculations of *Fink et al* were used in the model who considered ME as a gas pocket. Validation of the model is based on demonstrating similar time period range for induction of atelectasis, as was measured in the clinical study of *Luntz et al*. The model examined a diffusion-limited gas transport between mucosal blood and air in a closed ME, with constant partial gas pressures in the venous blood, and an inflammation-free ME. General Gas Law was applied to describe METP change. For improving this mathematical model [Kónya 2008], we examined pressure changes in the

ME due to periodic ET openings, considering different ME volumes. MatLab® Simulink program was applied for simulation.

Input data: Partial gas pressure values in human MEs and nasopharynx obtained experimentally by other authors as initial baseline values were used together with our previous 3D CT reconstruction data of normal and pathological MEs as ME volumes. The model settings were as follows: ET openings in every 90 sec as normal ET function, and 30 and 120 minutes opening intervals as transient or prolonged ET dysfunction; 0.1 sec airflow time per ET opening as minimally necessary time period to equalize pressure difference between ME and nasopharynx. The flow rate was automatically calculated from the partial gas pressure differences at the beginning of every ET openings. The model simulated an increase in the amount of gas entering the ME proportional to the atmospheric air (nasopharyngeal air) composition at every ET opening. The tympanic cavity and the MCS were considered as communicating cavities. The model included known values of the diffusion constants in a $V_{ME}=1\text{ ml}$ to calculate the diffusion coefficients in different ME volumes using a multiplying constant. The surface area-to-volume ratio was considered as a non-linear function of ME volumes in the model.

Validity of the model was supported by ME gas pressure values after a longer computer-generated program run stabilizing around the partial gas pressure values measured at steady-state in normal human MEs and by our previous 3D CT reconstruction findings in ears of healthy children and children with OME persisting more than a year as being consistent with the model predictions.

ME volume: Previously reported 3D CT reconstructions of temporal bones in children aged 2-18 years established the smallest healthy $V_{ME}\sim 3\text{ ml}$. Average healthy $V_{ME}=6.0\text{ ml}$. Children with persistent OME more than a year and with cholesteatoma show $V_{ME}\sim 1.7\text{ ml}$ and $V_{ME}\sim 1.1\text{ ml}$ on average, respectively.

Mastoid obliteration was simulated by eliminating the MCS, and taking only the $V_{ME}=0.6\text{ ml}$. The surface area in the postero-superior part of the TC, equivalent to epitympanum ($V_{ME}=0.2\text{ ml}$) was calculated for diffusion.

4.3 Comparative examination of the ME surface-to-volume ratio in healthy children aged 2-18 years, and age matched children with chronic OME

OME patients were divided into two groups based on the otoscopic findings. The composition of the groups was as follows. The healthy group consisted of 40 healthy children (74 MEs) described in point 4.1 (Group I). Of the 56 cases of persistent OME discussed in point 4.1, 49 children with OME persisting over a year (17 girls, 23 boys; mean age \pm SD: 7.1 \pm 3.1 years) made up Group II (92 MEs). Selection criteria were TM retraction, serous or mucous ME effusion with limited movement of the TM, as well as a B or C2 type tympanogram and insertion of at least one ventilation tube in the patient's history. Group III (39 MEs) contained 24 children (7 girls, 17 boys; mean age \pm SD: 10.3 \pm 3.8 years). Out of these patients, 17 had been treated previously in other institutions with OME persisting over a year. These children conformed to the criteria of Group II, and their TM showed segmental atrophy or pre-cholesteatoma (*Sade* grade II-IV). An additional 7 OME patients were assigned to this category from the chronic OME group in point 4.1 based on their otoscopic findings, showing *Sade II-IV* criteria. To evaluate the mastoid process, the 17 new children underwent cranial CT scans using the settings described in point 4.1. This was followed by a 3D CT reconstruction analysis to assess the surface area and volume of the ME. The surface area-to-volume ratio was calculated in the three groups and examined in the function of the ME volume. Statistical analyses were carried out using SPSS (Inc., Chicago, IL, U.S.A.) and BMDP (Inc., Los Angeles, CA, USA) software applications. Comparison of average ME volume, surface and surface-to-volume ratios was conducted in the three groups using Mann-Whitney tests.

4.4. Examination of the change in ME pneumatization of chronic OME cases after five years

The hospital CT database was searched for repeated CT scans of children from the Group II-III having treated with prolonged OME. It allowed assessing 3D CT reconstruction data in 20 ears of 10 children (3 girls and 7 boys, mean \pm SD: 10.60 \pm 3.85 years at the first CT scan), four from the Group II, as defined in point 4.3, and six from the Group III, after a five years follow-up.

The development of ME geometry (volume, surface area, surface area-to-volume ratio) and age at the first ventilation tube insertion were examined and compared with corresponding otoscopic findings from the medical reports of these children. Potential determinants of the mastoid growth and predictors in development of segmental atrophy or atelectasis were assessed.

Mann-Whitney-test was used to compare the ME surface area, volume and surface area-to-volume ratio in Groups I-III. Kendall and Spearman rank correlation was used to assess determinant factors in the development of mastoid geometry. Chi square test was applied to determine predictors of ME structural changes. Statistical analyses were performed using SPSS (Inc., Chicago, IL, USA) and BMDP (Inc., Los Angeles, CA, USA) statistical software. Statistically significant differences were considered at $p < 0.05$.

5. Results

5.1 Development of ME pneumatization in healthy children aged 2-18 years, and age matched children with chronic OME

The mean mastoid volume is *10.05 ml* (range, 3.95-28.34 ml; SD, 5.3 ml) in the healthy group and *2.82 ml* (range, 0.29-9.27 ml; SD, 1.51 ml) in the OME group. The mean surface area of the MCS in the healthy group was *84.47 cm²* (range, 29.59-217.69 cm²; SD, 37.95 cm²), and it was *40.45 cm²* (range, 2.93-122.18 cm²; SD, 18.14 cm²) in the OME group. The differences between the healthy and the OME group are statistically significant ($p < 0.0005$). Correlations of the volume and surface area of the right and left sides in the healthy group were $r = 0.97$ (volume) and $r = 0.94$ (surface). In OME patients, these are $r = 0.78$ for volume and $r = 0.89$ for surface. Patients with OME exhibited a larger difference in volume of the left and right MEs. Surface-to-volume values of the ears highly correlated in the healthy group and in the OME group as well (healthy, $r = 0.89$; OME, $r = 0.94$).

Both mean surface and volume of MCS differ significantly in the age groups of healthy and OME patients. Development of the healthy MCS is continuous until the age of 7 to 8 years, and then it slows down temporarily, after which quick growth once again returns after the age of 9 to 13 years. Before the age of 9 to 13 years, no substantial difference is found between the surface and

volume of healthy MCS in boys and girls. After the age of 9 to 13 years, girls' MCS develops faster. This is obvious during puberty.

Children in the healthy group aged 2 to 4 years have an average surface area of 45.65 cm^2 . This is 114.72 cm^2 in the 14 to 18-year-old group. Volume averages are 5.4 and 15.0 ml , respectively. The average surface area in the OME group is 36.65 cm^2 in the age range of 2 to 4 years and 52.53 cm^2 in the age range of 14 to 18 years. Average volume is 2.52 and 3.63 ml , respectively. ME surface and volume of healthy and OME children differ significantly. Latter parameters are lower, and developmental rate is very low. Intractable OME cases have the lowest ME parameters. The difference between the mean ME surface area and volume of OME patients and those of intractable OME patients is significant ($p < 0.0028$ and $p < 0.0005$). Healthy and OME ears clearly show a difference -especially for the ME volume- and are separated from each other by the value of 5 ml . In intractable OME cases between 2 and 4 years of age, the average volume of the ME is 2.12 ml , whereas the average surface is 33.61 cm^2 . The corresponding averages for ages 14 to 18 are 1.91 ml and 35.20 cm^2 . The results show that in MEs with structural lesions of the TM, the ME volume is 2 ml or less.

5.2 ME gas pressure regulation

(For the assessment of the model estimates, it must be taken into consideration that the 3D CT reconstruction measurements were primarily aimed to compare the bony structure of the healthy and mucous filled MEs. The adequate setting disrespects mucus or soft tissue content and mucosal lining, thus slightly overestimates the actual volume and surface area of the air containing ME. The latter volume values are ~40% lower than data indicated in point 5.1, whereas surface values are ~25% lower. To facilitate the interpretation of the model estimates, volume values of the bony ME structure are followed by the air content values, in parentheses).

5.2 ME pressure change when ET is closed

Following the closure of the ET, initially METP increases. A slow decrease follows below the atmospheric pressure. Similar METP values develop much earlier in a $V_{ME}=1 \text{ ml}$ than in a $V_{ME}=3-10 \text{ ml}$. The largest time difference can be established between the $V_{ME}=1 \text{ ml}$ and $V_{ME}=3 \text{ ml}$ as to reach the critical - 333.3 daPa (-25 mmHg) pressure value relative to ambient when effusion enters the ME from blood vessels due to the increased capillary permeability.

5.2.2 ME pressure changes when ET opens periodically (normal ET condition)

Transmucosal gas exchange results in METP decrease between two ET openings, which compensated by airflow through the ET in every 90 sec. It results in a dynamic pressure balance, which is stabilized at 16 daPa (1.2 mmHg) pressure fluctuations in the $V_{ME}=1 \text{ ml}$. This is 6.66 daPa (0.5 mmHg) in a $V_{ME}=3 \text{ ml}$ and 5.3 daPa (0.4 mmHg) in a $V_{ME}=10 \text{ ml}$.

5.2.3 ME pressure changes with ET dysfunction

Transient and prolonged ET dysfunction was simulated by taking longer intervals between two ET openings (Fig. 3). When the ET opens every 30 or 120 minutes only the ME pressure fluctuations are one order of magnitude higher than in 90 second ET openings. The pressure fluctuations are 173.3 daPa (13 mmHg)/ $V_{ME}=1 \text{ ml}$, 119.9 daPa (9 mmHg)/ $V_{ME}=3 \text{ ml}$ and 93.3 daPa (7 mmHg)/ $V_{ME}=10 \text{ ml}$ in the case where ET opens every 30 minutes. Larger pressure decreases of 466.6 daPa (35 mmHg), 373.3 daPa (28 mmHg), and 266.6 daPa (20 mmHg) apply respectively, when the ET opens only in every 120 minutes.

5.2.4 ME pressure balance after obliteration of the mastoid

Mucosal surface area of the postero-superior part in a $V_{ME}=0.6 \text{ ml}$, corresponding to the surface area of a 0.2 ml volume (epitympanum) serves for gas exchange. In a $V_{ME}=0.6 \text{ ml}$ the dynamic pressure balance is stabilized at 5.3 daPa (0.4 mmHg) pressure fluctuations when ET function is good. Transient and prolonged ET dysfunction result in similar periodic pressure changes than that of a larger ($V_{ME}>3\text{ml}$) ME with 66.6 daPa (5 mmHg) and 266.6 daPa (20 mmHg) pressure fluctuations. Pressure fluctuations decrease further when epitympanum is also obliterated.

5.3 The ME surface-to-volume ratio in healthy children aged 2-18 years, and age matched children with chronic OME

Between the ages of 2 and 18 years, the average surface-to-volume ratio of children with chronic OME (Group II) was significantly higher ($14.62/\text{cm}$) than that of healthy children (Group I, $8.79/\text{cm}$; $p=0.0000$). The average surface-to-volume ratio of intractable OME cases (Group III) proved to be the highest ($14.90/\text{cm}$). There was no significant difference between the average values

of Groups II and III ($p=0.783$). The surface-to-volume values decrease as the ME volume increases. This correlation follows a non-linear, negative function ($y=17.577x^{-0.283}$). The surface area-to-volume ratio does not change by age in both healthy and OME children. Its value is significantly greater ($p < 0.0005$) for the OME group than in the healthy group.

5.4 Development of ME pneumatization over five years in children with chronic OME

In 11 ears the ME volume increased and did not change in one ear. However, the growth rate was much lower than that of the healthy ears and reached the $V_{ME}=5.3 \text{ ml}$ (3.2 ml), typical minimal ME volume of healthy children only in four ears. In 8 ears the ME volume decreased by age. The correlation between the initial and final ME volume values after a five years follow-up, and between the initial and final surface area values was excellent ($r=0.7850$, $p=0.0000$; and $r=0.8105$, $p=0.0000$; respectively). There was a significant negative correlation between the initial ME volume, initial surface area and *Sade grade III-IV* otoscopic picture after the five-years follow-up ($r=-0.7752$, $p=0.0001$; $r=-0.6988$, $p=0.0006$; respectively). The correlation between the initial surface area-to-volume ratio and the development of *Sade grade III-IV* otoscopic picture after five years was $r=0.4789$, $p=0.0327$. The mastoid growth was predicted with 84.2% confidence by the following three factors: *younger age than 6 years* at the first grommet insertion, initial $V_{ME}>3.38 \text{ ml}$ ($>2 \text{ ml}$) and *Sade grade I-II* initial otoscopic picture. The initial $V_{ME}<2 \text{ ml}$ ($<1.2 \text{ ml}$) was a strong predictor in the development of *Sade grade III-IV* otoscopic picture ($\text{Chi}^2 \text{ test}=18$, $p=0.0004$). In ears with final $V_{ME}>2.5 \text{ ml}$ ($>1.5 \text{ ml}$) the surface-to-volume ratio decreased and did not change in smaller MEs.

6. Discussion

6.1 Development of ME pneumatization in healthy children aged 2-18 years, and age matched children with chronic OME

This is the first 3D CT comparative study performed on a larger pediatric population, collecting ME surface area and volume data from healthy and chronic OME children. Our results show that children with chronic OME have significantly smaller ME surface area and volume than healthy children. The average ME volume of the healthy group between 2-4 years was $V_{ME}=5.3 \text{ ml}$

(3.2 ml). The ME surface area and volume of healthy children have continuous extension up to 18 years. The average ME volume in this age group was $V_{ME}=10.0 \text{ ml}$ (6.0 ml). Following a temporary slow down, the ME pneumatization has a faster rate around puberty, and reaches an average of $V_{ME}=14.94 \text{ ml}$ (9.0 ml) with a variable dimensions among individuals.

Rubensohn examined 413 ears of children between one and 15 years with planimetric method and found that the mastoid pneumatization process of girls ends at the age of 10 years and at the age of 15 years in boys. Our healthy ME data show different developments. There is no substantial difference between the ME pneumatization process of boys and girls until the age of 7-8 years. The growth rate becomes faster during puberty in both genders and the final surface area and volume of ME are larger in girls by the age of 18 years. At the beginning, most of the pneumatized bone cells are in the squama of the temporal bone. The antrum is well developed at birth. After birth, MCS formation continues in infants resulting in different individual sizes.

Diamant suggested that the MCS development is a genetically determined process. According to *Tos, Palva and Palva, Flisberg and Zsigmond*, and *Bluestone*, normal development can be restricted by several environmental factors (toxins, amnion cells, and exogenous substances). Clinical observations and our supporting 3D measurement data have confirmed that OME in children associated with smaller ME volume and a slight growth of mastoid cellularity can only be seen during puberty. Our data also show that the mean ME surface value of the 14 to 18-year-old chronic OME group only reaches the mean value of 2 to 4-year-old healthy group, and the mean ME volume in OME cases remains below. The extension of cellularization is presumably arrested in these children by inflammation in the ME cleft. It was justified histologically by *Palva and Palva* that ME infections cause sclerosis in the mastoid cells in early age and block further increase in cellularization despite a simultaneously normal ET function. Infections in a well-developed ME cause accumulation of granulation tissue. This will be converted into dense acellular bone later on. Small mastoid cellularization can hence be the result of previous ME infections and subsequent bone formation. According to *Rüedi's* research, persistent negative ME pressure after infection and the presence of middle ear effusion block the mastoid pneumatization process. It

was shown by longitudinal studies of *Aoki* that pathologic lesions of the ME lamina propria disrupt the ME gas exchange. Weak ME pneumatization shows a strong correlation with the severity of otitis media in the patient's history. *Aoki* demonstrated that after 2 months of ventilation tube insertion the swelling of the mucous membrane in the ME eliminated. However, in cases of severe mucosal lesion, up to 1.5-2 years may be necessary to increase ME pneumatization, which follows by the normalization of the histopathological changes and gas exchange. Using 2D planimetric examinations, *Valtonen* concluded that the insertion of a ventilation tube at a young age promotes the ME pneumatization. In the majority of our cases with chronic OME, the ME was almost completely filled with mucus or granulation tissue. According to our findings, ME surface and volume did not increase significantly between 2 and 18 years in OME children. In OME patients, because of disrupted pneumatization process, bony cells can only be found mainly around the antrum.

6.2 Mathematical modeling of gas pressure regulation in healthy and pathologic MEs

6.2.1 Pressure changes in the ME with normal and pathologic ET function

This is the first study that examined the development of METP changes in the function of different ME volumes, considering normal and dysfunctional ET. The model estimates showed that in perfect ET function in $V_{ME}=1\text{ ml}$ still results in much greater METP fluctuations than in $V_{ME}\geq 3\text{ ml}$. Transient or prolonged ET dysfunction cause pressure fluctuations of an order of magnitude larger. These are inversely proportional to the ME volume. It is generally accepted that poor ET function and ME gas pressure deregulation are associated with TM and ME pathologies (OME, segmental atrophy of the TM, atelectasis, ossicular chain disruption and cholesteatoma). The ME cavity is a relatively rigid gas pocket. Gas containing cavities in the body usually exist as long as they have connection to the gas source. The periodic ET openings, due to swallowing, enable the ME cavity to replenish itself with air and maintain a steady state balance. The TM as an active pressure buffer also contributes to METP control; however, its role is limited to compensate

for small, sudden pressure changes. The ME volume serves as a pressure buffer and the mucosal surface serves as gas exchanger. Considering that gas flow rate is directly proportional to the extent of the surface area during the passive gas exchange, the rate of METP decrease depends on the surface area-to-volume ratio. The surface area-to-volume ratio of any geometric shapes decreases as the volume increases. This relationship can be described as a non-linear function. It is known that the sphere has the smallest surface area-to-volume ratio. The value is greater for all geometric shapes different from sphere. It can be assumed that surface-to-volume ratio is the highest in small volume MEs. Consequently, the rate of METP change due to gas exchange is the fastest here. The model results show substantial differences in magnitude of the METP fluctuations between a $V_{ME}=1\text{ ml}$ and $V_{ME}\geq 3\text{ ml}$. Modeling a perfect ET function, the METP fluctuations are small (16 daPa, 6.66 daPa and 5.33 daPa in a $V_{ME}=1\text{ ml}$, 3 ml and 10 ml, respectively) when the periodic ET openings of every 90 seconds on average are performed in healthy ears. Modeling transient and prolonged ET dysfunction, the METP fluctuations become larger with increased time intervals between two ET openings which are inversely proportional to the ME volume.

Normally, the pars flaccida flips in a very small range ($\pm 20\text{ daPa}$) (1.5 mm Hg) around pressure equilibrium. At higher negative METP, relative to ambient, pars tensa can be involved to compensate for pressure changes. The pars tensa is maximally displaced at about -50 daPa (3.75 mmHg) relative to ambient. This pressure value can be achieved much earlier in a $V_{ME}<5\text{ ml}$ (<3 ml) with malfunctioning ET. According to the model, in the case of transient ET dysfunction, where ET opens every 30 minutes, pressure fluctuations of 120.0 daPa (9 mmHg) and 173.31 daPa (13 mmHg) may initiate structural changes of the TM in smaller $V_{ME}=3\text{ ml}$ and 1 ml, respectively. At prolonged ET dysfunction in smaller $V_{ME}=3\text{ ml}$ and 1 ml MEs, increased pressure fluctuations exceed the critical METP relative to ambient and middle ear effusion enters the ME from blood vessels. MCS volume, extent and duration of ET dysfunction, which can differ individually, are determinant in initiating ME pathology and in clinical course. Our 3D CT reconstruction data of healthy and pathological temporal bones show a strong correlation with the

mathematical model estimates. The results show that the average ME volumes in healthy children aged 2 to 4, and 2 to 18 are $V_{ME}=5.3 \text{ ml}$ (3.2 ml) and $V_{ME}=10.0 \text{ ml}$ (6.0 ml), respectively. Cases with chronic OME and those with intractable OME showed the lowest average volumes at $V_{ME}=3.1 \text{ ml}$ (1.9 ml) and $V_{ME}=1.8 \text{ ml}$ (1.1 ml), respectively.

The results of the study reveal that gas exchange in $V_{ME}<5 \text{ ml}$ (<3 ml) differs from those of $V_{ME}\geq 5 \text{ ml}$ ($\geq 3 \text{ ml}$). Smaller MEs of $V_{ME}<5 \text{ ml}$ (<3 ml) suffer from larger METP fluctuations between two ET openings as compared to larger MEs due to faster gas exchange and reduced buffer capacity. Contrary, larger MEs has slower gas exchange and nearly constant METP. Healthy ears with a $V_{ME}>5 \text{ ml}$ (>3 ml) can even tolerate longer periods of ET dysfunction (>120 min) while maintaining gas pressure balance. The average ME volume of the healthy MEs in the 2 - 4 years age group have a typical $V_{ME}=5.3 \text{ ml}$ (3.2 ml) and are very sensitive to a potential ET dysfunction. At this age, ET dysfunction is quite common and may easily lead to the disruption of gas pressure balance. The results are consistent with clinical experience considering chronic otitis media and cholesteatoma.

6.2.2 Effect of mastoid obliteration on ME gas pressure balance

In the model situation of mastoid obliteration, the gas exchange is limited to the mucosal surface of the postero-superior part of a $V_{ME}=0.6 \text{ ml}$ only. This corresponds to the mucosal lining of a 0.2 ml volume (epitympanum). According to the model estimates, disproportionate reduction in the gas exchange surface area as compared to the entire surface area results in similar ME pressure changes to $V_{ME}\geq 3 \text{ ml}$ with both normal and malfunctioning ET. The obliteration of the mastoid and the epitympanum eliminates the mucosal surface area responsible for gas exchange. Thus, improves the functional surface-to-volume ratio. Consequently, it can be curative against larger pressure decrease in small MEs with poor ET function. Therefore, in cases of mastoid obliteration, gas pressure balance can be achieved even in MEs with 0.6 ml volumes, which is significantly lower than $V_{ME}=3 \text{ ml}$, by limiting the mucosal surface for gas exchange. This situation can be considered as a surgical adaptation of the ME gas pressure balance to the limited outer gas supply due to prolonged ET dysfunction. As a result,

development of ME pathology and long-term changes in TM behavior can be limited. The model data are also consistent with *Doyle's* opinion that the effective pressure buffering function does not require too large ME volume. The results of our modeling show that it is primarily a function of extent of the gas exchange surface.

The model presented here supports the hypothesis that in cases of acquired paediatric cholesteatoma, where MCS has lost its pressure buffer role and ET is dysfunctional, surgical reduction of the mucosal surface for gas exchange can promote maintenance of a steady state condition, thus lowering the recurrence rate and improving long-term surgical outcome. Nevertheless, these ears remain unprotected against sudden environmental pressure variations. Assuming the same pathomechanism in atelectatic ears, volume of the MCS should be considered in selecting candidates for mastoid obliteration.

6.3 The ME surface-to-volume ratio in healthy children aged 2-18 years, and age matched children with chronic OME, in relation to clinical course

The comparative examination of ME surface-to-volume ratio in healthy children aged 2 to 18 years and age matched children with chronic OME showed that in cases of chronic OME the surface-to-volume ratio is significantly higher than in healthy MEs. The surface-to-volume ratio decreases as the ME volume increases following a non-linear relationship. Consequently, the magnitude of the METP fluctuations between periodic ET openings progressively decreases as ME volume increases. It is consistent with the results of the current mathematical model estimates and supports the protective effect of larger MEs to develop chronic OME and atelectasis. The MCS constitutes the largest volume of the ME and has a passive pressure buffer role. The results also show that due to its large mucosal surface area and decreasing surface area-to-volume ratio with increasing ME volume, it also acts as a rate-limiter of the METP decrease. Calculations indicate that healthy ears are separated from the ears of children with chronic OME both by the surface-to-volume ratio $\sim 10.0/cm$ and by the $V_{ME} \sim 5 ml$ (3 ml). The latter has also been supported by two previous studies. In most cases of persistent OME the ME volume is below $V_{ME} < 5 ml$ (<3 ml), and the surface-to-

volume ratio is $>10.0/cm$. Data of this study suggest that ears with $V_{ME} \geq 10 \text{ ml}$ ($>6 \text{ ml}$) show stable gas pressure balance due to larger volume and smaller surface-to-volume ratio. The model estimates support that - at normal ET function - in MEs between $V_{ME}=5-10 \text{ ml}$ (3-6 ml) lower pressure fluctuations resulting from gas exchange are compensated by the TM compliance. This is a consequence of passive pressure buffer effect of MCS and a low surface-to-volume ratio. However, as the ME volume decreases, the passive pressure buffer function of MCS reduces. Faster gas exchange results in larger METP fluctuations and a larger strain on the TM as an active pressure buffer. These MEs - typically with a $V_{ME} < 5 \text{ ml}$ ($<3 \text{ ml}$) - require frequent ET opening to maintain normal ME function and hearing. The pressure fluctuations are close to the buffer capacity of the pars tensa. Transient ET dysfunction results in pressure decrease in these ears limited by the capillary hydrostatic pressure when effusion accumulates in the ME decreasing the ME volume and the surface area for gas exchange. If ET dysfunction recovers, the ME effusion eliminates and gas pressure balance restores. At prolonged ET dysfunction effusion may also contribute to chronic granulation, which ultimately results in ossification of the bony MCS, narrowing the ME volume and reducing the surface area. However, the surface area-to-volume ratio remains high. As a consequence, chronic otitis media may develop due to faster gas exchange in a small ME with a malfunctioning ET. These mechanisms can be considered as a partial adaptation of the ME gas pressure balance to the limited outer gas supply due to prolonged ET dysfunction. In rare cases MEs as large as 9.2 ml (5.5 ml) can develop OME in prolonged ET dysfunction and ears between $V_{ME}=5-10 \text{ ml}$ (3-6 ml) may have normal ME gas pressure balance even with a slightly higher surface area-to-volume ratio than $10.0/cm$ when the ET function is good. It was confirmed by *Shimada* in a comparable cohort of patients that individuals with extreme ET dysfunction had the weakest mastoid pneumatization and the number of postoperative failures related the TM was the highest in this category. Comparative study of *Sade* performed on atelectatic and sclerotic ears also supports the positive association between atelectatic ears and weak mastoid pneumatization. In a previous study, we demonstrated that in MEs with *Sade III* grade otoscopic picture, excision of the pars tensa retraction pocket and simultaneous insertion of ventilation tube

is less effective in the long term as in cases of *Sade II* grade MEs. The findings of this study are also consistent with the mathematical equations described by *Doyle* and *Swartz* previously to define the rate limiting function of the ME during gas exchange at different volumes. The results also indicate that ME pathological changes especially develop in ears with a mean $V_{ME}=1.8$ ml (1.1 ml) and a mean surface area-to-volume ratio of $14.9/cm$. These data support the validity of the mathematical model estimates of gas exchange in healthy and pathological MEs. Given these findings, ME volume is determinant in the development of TM structural lesions.

6.4 Development of ME pneumatization over five years in children with chronic OME

This is the first study that introduces ME volume and surface area data after a five-year follow-up using 3D CT reconstruction of temporal bones in children with OME persisting more than a year and underwent at least one ventilation tube insertion during this period. Potential determinants of ME development and predictors of TM structural lesions and atelectasis formation in ears of children with chronic OME were also reconsidered in this study. The results show that the ME volume increased in 55% of the ears during the five-years follow-up, however, it remained below 5 ml (3 ml) in 91% of ears and exceeded the 5 ml (3 ml) ME volume in only 5% presenting normal otoscopic appearance after five years. In 40% of prolonged OME cases the ME volume decreased with time. The findings support that chronic inflammation may hamper the mastoid growth, and granulation tissue can convert into dense acellular bone, which suggest the role of environmental factors in the MCS development in cases of persistent OME.

The results also indicate that initial ME volume, surface area and the surface area-to-volume ratio are important variables in the development of the ME cleft. The initial $V_{ME}<3.38$ ml (<2 ml), the surface area <40.0 cm^2 and surface area-to-volume ratio $>14.0/cm$ were good predictors of the development of *Sade grade II-IV* otoscopic picture, ossicular chain disruption and cholesteatoma formation after a five years follow-up. The incidence of segmental atrophy and atelectasis was significantly higher in $V_{ME}<3.38$ ml (<2 ml) than in $V_{ME}>3.38$ ml (>2 ml) ($p=0.0004$). As the ME volume increased the

surface area-to-volume ratio decreased in ears with $V_{ME} > 2.50 \text{ ml}$ ($> 1.50 \text{ ml}$). The analysis data based on 20 ears support that the effect of ventilation tube insertion on ME growth is closely related to the age ($< 6 \text{ years of age}$), the initial ME volume of $> 3.38 \text{ ml}$ ($> 2.0 \text{ ml}$) and the initial surface-to-volume ratio ($< 14.0/\text{cm}$). The initial surface-to-volume ratio and ME volume along with duration of ET dysfunction determine the extent of ME pathological changes. These data support that the rate of ME pressure change also depends on the surface-to-volume ratio which is ultimately a function of the ME volume. Given these findings, ME volume can be important factor in surgery of chronic otitis media.

7. Summary and new results

1. This is the first study to publish comparative cross-sectional 3D CT reconstruction data on the development of ME volume, surface area and surface-to-volume ratio in healthy children aged 2 - 18 years and children with chronic OME persisting over a year. We concluded that
 - a) the volume and surface area of healthy MEs show continuous growth, albeit with a variable intensity between the ages of 2 -18 years;
 - b) before the age of 9 to 13 years, no substantial difference is found between the surface area and volume of healthy MCS in boys and girls. After the age of 9 to 13 years, girls' MCS develops faster. The final surface area and volume of MCS are larger in girls by the age of 18 years.
 - c) in cases of chronic OME, the ME volume and surface area values are significantly lower than in healthy children;
 - d) intractable OME cases have significantly lower average ME volume and surface area values as compared to chronic OME cases;
 - e) the surface-to-volume ratio does not change by age in both healthy and OME children. Its value is significantly greater for the OME group than in the healthy group;

- f) the surface-to-volume ratio of the ME decreases as the ME volume increases following a non-linear relationship;
2. This is the first study that apply mathematical modeling to show that the gas pressure balance of $V_{ME} \geq 3$ ml, characteristic of healthy children between 2 - 18 years differs from that of $V_{ME} < 3$ ml, typical in chronic OME cases.
 3. It was determined that stable gas pressure balance of $V_{ME} > 6$ ml provides protective effect to develop ME pathology. This fact is partly due to the larger gas volume and partly to the slower gas exchange and METP change resulting from the smaller surface-to-volume ratio.
 4. Furthermore, it was confirmed that gas pressure balance of MEs between $V_{ME} = 3-6$ ml are very sensitive to the duration of a potential ET dysfunction to initiate ME pathology.
 5. This is the first study to show in a mathematical model situation that mastoid obliteration can be curative against larger pressure decrease in small MEs, where MCS has lost its pressure buffer role and ET is dysfunctional, by a disproportionate elimination of the mucosal surface area for gas exchange. Thus, it can promote maintenance of a steady state condition, lowering the recurrence rate and improving long-term surgical outcome.
 6. The current study was the first to present 3D CT reconstruction data on the development of ME pneumatization in chronic OME cases after five years. The data support that chronic OME has a negative impact on the ME pneumatization. Furthermore, it was highlighted that $V_{ME} < 5$ ml (<3 ml) has a critical role in the onset of pathological processes.

7. Clinical application of the results

7.1 Mathematical modeling provides a possibility of a new pathophysiological oriented approach in the therapy of chronic otitis media including individualized surgical solutions. This method has the potential to revolutionize otomicrosurgery, offering solutions to the previously unresolved issues in the therapy of chronic otitis media. The results of the current study indicate that in cases of retraction cholesteatoma where ET is dysfunctional and the $V_{ME} < 2 \text{ ml}$, mastoid obliteration may contribute to the long term stabilization of ME gas pressure balance and the restoration of normal ME function. Assuming the same pathomechanism in atelectatic ears, volume of the MCS should be considered in selecting candidates for mastoid obliteration.

7.2 Clinical experience shows that ET dysfunction is very common in early childhood between 2-4 years of age with a high incidence of OME. ET function can improve in time remaining permanently poor in only rare cases. Measurement data of this study indicate that the average ME volume typical in healthy children aged 2-4 years is in the critical 3-6 ml range. Thus, these children are most at risk to develop early ME pathology during a potential ET dysfunction.

Considering the results of five-year follow-up and relevant literature data, grommet insertion between 2-4 years of age can be advantageous to promote mastoid pneumatization in prolonged OME cases (after 3 months) by changing ME geometry. Elimination of inflammation in the ME mucosal lining can normalize the gas exchange and restore the ME pneumatization process. Increase in volume by optimizing the ME geometry is one of the determining factors in stabilization of ME gas pressure balance. The data also indicate that positive effect of the ventilation tube on ME growth is less pronounced after 6 years of age. However, further prospective studies on a larger sample of chronic OME patients having ventilation tubes inserted are necessary to support the latter finding.

8. PUBLICATIONS



UNIVERSITY OF DEBRECEN
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PUBLICATIONS



Register number: DEENKÉTK/87/2014.
Item number:
Subject: Ph.D. List of Publications

Candidate: Zsuzsanna Csákányi
Neptun ID: EXTT1N
Doctoral School: Doctoral School of Neurosciences

List of publications related to the dissertation

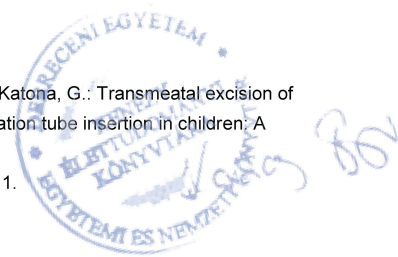
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Total IF of journals (publications related to the dissertation): 5.268

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