Eustachian tube function

some pathophysiological aspects and effects of intervention

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Eustachian tube function

some pathophysiological aspects and effects of intervention

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op het gebied van
de Medische Wetenschappen

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tu remanebis amicus maximus perpetuo

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Chapter 1

Introduction

More than 2500 years ago Alcmaeon of Sparta already assumed that the middle ear and the respiratory tract were connected by an open pathway.[1] In 1562 this connection between the middle ear and the nasopharynx was named after Bartholomeus Eustachius, an Italian anatomist who gave a detailed description of the Eustachian tube in his thesis, "Epistola de Auditus Organis".[2] In the following centuries Valsalva, Toynbee, Politzer and many other physicians studied the Eustachian tube. They all contributed to the current concept of the Eustachian tube and its function with respect to the middle ear. However, the Eustachian tube partly remains a mystery as will turn out later.

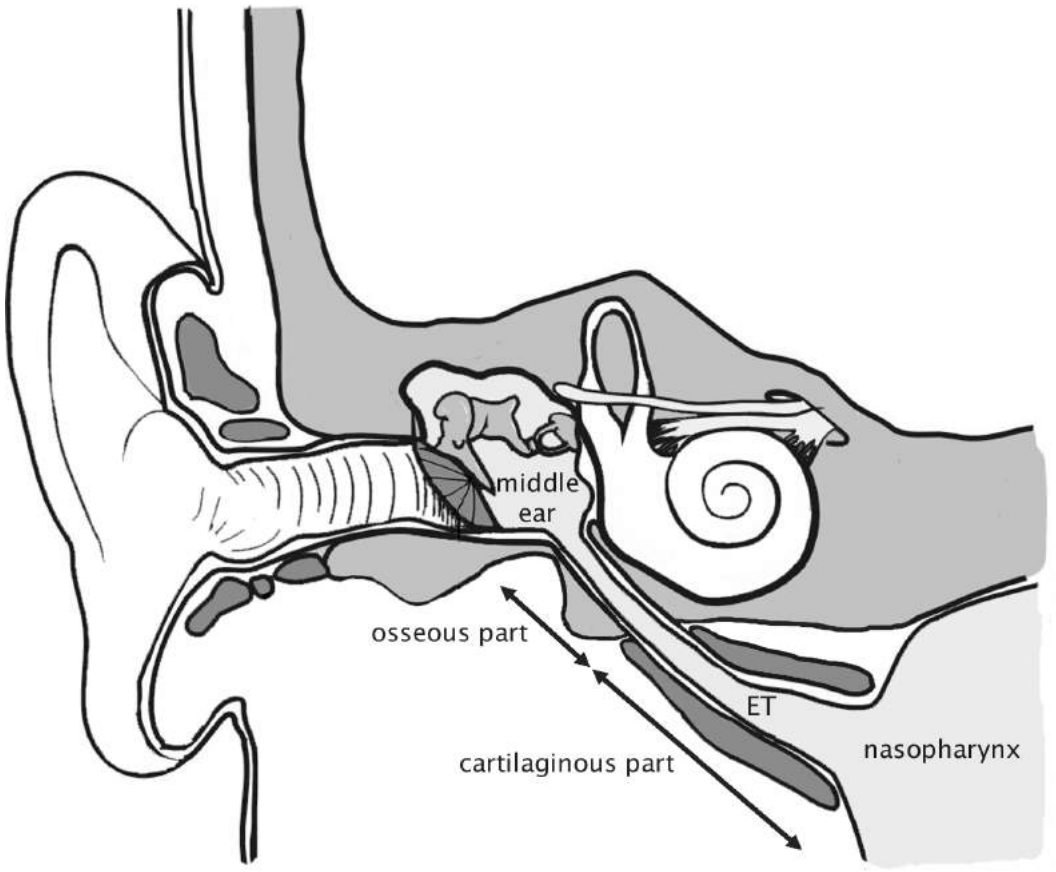

Figure 1. Anatomy of the Eustachian tube (ET).

Anatomy & Morphology

The Eustachian tube connects the middle ear with the nasopharynx, as shown in Figure 1. From the middle ear the adult Eustachian tube extends anteriorly, medially and inferiorly to the nasopharynx at an angle of 30 to 40 degrees with the horizontal plane.[3] In adults, the total length of the Eustachian tube varies from 31-38 mm.[4] The posterolateral one third of the Eustachian tube is fixed and has an osseous wall, whereas the anteromedial two thirds are mobile and is

surrounded by a fibrocartilaginous wall. The superior and medial part of the fibrocartilaginous wall consists of cartilage, while the lateral part is composed of a firm fibrous sheet. Both the osseous and the cartilaginous parts are shaped like a cone, with their apices pointing towards each other. At rest, the fibrocartilaginous part of the Eustachian tube is collapsed and forms a slit-like funnel. The osseous and fibrocartilaginous parts are connected at the isthmus. The isthmus is the narrowest point of the Eustachian tube with an average diameter of 2.5 to 1.5 mm in adults.[5]

Several muscles are closely related to the Eustachian tube, anatomically as well as functionally: the tensor veli palatini muscle, the levator veli palatini muscle, the salpingopharyngeus muscle and the tensor tympani muscle. The tensor veli palatini muscle originates from the superior cartilage and the lateral fibrous wall of the Eustachian tube, bends round the pterygoid process and continues as the palatal aponeurosis. The tensor veli palatini muscle is considered to be the main dilator of the Eustachian tube. The levator veli palatini muscle that partially originates from the medial portion of the Eustachian tube cartilage and inserts into the soft palate is supposed to support the Eustachian tube opening. The salpingopharyngeus muscle, running from the medial cartilaginous wall to the pharyngeal wall, and the tensor tympani muscle that is continuous with the tensor veli palatini muscle are relatively small and only seem to play a marginal role in Eustachian tube opening.[6-8]

The anatomy of the infant Eustachian tube is remarkably different from the anatomy of the adult Eustachian tube. In children, the angle of the Eustachian tube with the horizontal plane is 10 instead of 30 to 40 degrees.[3] In children the Eustachian tube is also shorter, with a relatively longer osseous part,[9] and has a smaller lumen.[10] In addition, the mean density of elastin in the Eustachian tube cartilage is significantly smaller in children than in adults.[11]

The Eustachian tube is lined with epithelium of variable thickness. The osseous part is lined with thin columnar ciliated epithelium that is continuous with strands of ciliated epithelium in the middle ear cavity. The epithelium in the fibrocartilaginous part that is continuous with the respiratory epithelium of the upper respiratory tract is thicker and pseudostratified. It is composed of columnar cells, many of which are ciliated. Cilia are contractile organelles. Contraction of these organelles results in a beating or sweeping movement. Near the nasopharyngeal orifice, many goblet cells and small glands can be found.[12] These goblet cells and small glands produce mucus that forms a “micron”-thick mucus blanket. This mucus blanket covers the epithelium of the Eustachian tube and is very important for the mucociliary transport.[13] The subepithelial

connective tissue of the Eustachian tube contains numerous blood capillaries, lymph capillaries, nerve fibres and mucosa-associated lymphoid tissue.[14,15]

Physiology

The Eustachian tube has three important functions with respect to the middle ear: ventilation, protection and clearance.

Ventilatory function

In the middle ear, gases are continuously exchanged between the middle ear cavity and the surrounding tissues. This gas exchange is a bi-directional process.[16,17] Under normal conditions, the resultant changes in middle ear pressure are relatively small. Frequent active opening of the Eustachian tube allows ventilation of the middle ear cavity and equilibration of these small pressure differences. Active opening of the Eustachian tube is accomplished by contraction of the paratubal muscles during swallowing, yawning or movement of the mandible. Eustachian tube opening is assumed to be facilitated by a mixture of surfactant proteins[18,19] and surface tension lowering phospholipids, especially phosphatidylcholines and sphingomyelins,[20,21] that are secreted into the mucus by the Eustachian tube epithelium. Together they are referred to as Eustachian tube surfactant. Eustachian tube surfactant is supposed to act as a release agent by preventing solid-to-solid adhesion.[22]

Protective function

At rest, the Eustachian tube lumen is closed. The closed Eustachian tube offers protection against nasopharyngeal pressure variations and ascending secretions and micro-organisms. When the Eustachian tube opens, secretions can enter the nasopharyngeal end of the Eustachian tube, but they can not gain access into the middle ear, due to the narrow midportion of the Eustachian tube, the isthmus.[23] The Eustachian tube mucus that is constantly produced by the Eustachian tube epithelium also acts as a physical barrier.

In addition to this “mechanical” protection, the Eustachian tube also protects the middle ear against invading pathogens by several local immunological defence mechanisms.[24,25] This aspect of Eustachian tube function is not limited to the Eustachian tube alone but is part of the local immune system of the upper respiratory tract. Especially the adenoid is important in protecting the host against invasion of pathogens into the Eustachian tube and middle ear.[26] The presence of viruses, bacteria or bacterial products in the Eustachian tube or middle ear stimulates the production of effector and memory lymphocytes in the

mucosa-associated lymphoid tissue of the Eustachian tube.[27,28] Different types of effector lymphocytes are involved in initiation and augmentation of the inflammatory response, lysis of antigenic target cells (e.g. macrophages), and production of antibodies. One subclass of these antibodies is secreted into the Eustachian tube mucus (secretory IgA). Secretory IgA inhibits bacterial adherence and reduces bacterial colonisation.[14] Surfactant proteins are also part of the local defence against pathogens, in addition to their ability to facilitate Eustachian tube ventilatory function. They play a role as opsonins for facilitating phagocytosis.[29] Besides secretory IgA and surfactant proteins, the Eustachian tube mucus contains other anti-microbial molecules like complement factors, lysozyme, lactoferrin and beta-defensins.[18,27,30] The synthesis of memory lymphocytes enables an increased immunological response when exposure to the same antigen occurs again. The presence of pathogens in the Eustachian tube also stimulates the synthesis of cytokines. Cytokines are secreted by macrophages, monocytes or lymphocytes and orchestrate the immune response.[31] For example, they induce chemotaxis of polymorphonuclear leukocytes. The primary function of the polymorphonuclear leukocytes is phagocytosis and intracellular killing of invading micro-organisms.

Clearance function

The Eustachian tube has two methods of clearance: mucociliary clearance and muscular clearance. The mucociliary epithelium of the Eustachian tube is responsible for mucociliary clearance of the middle ear. Together with the mucus blanket that covers the epithelium of the Eustachian tube secretions and debris from the middle ear are transported towards the nasopharyngeal end of the Eustachian tube by the synchronised movement of the cilia.[32] Both cilia and mucus are essential for normal mucociliary transport. Any disturbance of either the cilia or the mucus may immediately affect normal mucociliary clearance.[33,34] The pumping action of the Eustachian tube (muscular clearance) also expels secretions from the middle ear.[35,36] During active opening of the Eustachian tube by contraction of the paratubal muscles, the tubal lumen enlarges and excess secretions are sucked into the Eustachian tube. Relaxation of the paratubal muscles and subsequent closure of the Eustachian tube cause the assembled fluid to be pumped towards the nasopharyngeal end of the Eustachian tube. Repeated opening and closure of the Eustachian tube finally clears the secretions into the nasopharynx. Secretions are particularly cleared from the middle ear by this muscular clearance when their volume is large.[36]

Measurement of Eustachian tube function

Ever since the importance of the Eustachian tube with respect to the middle ear is recognised, clinicians and investigators have been interested in measuring the Eustachian tube function. Several test methods have been and still are being used to study the ventilatory, protective and clearance function of the Eustachian tube.

Measurement of ventilatory function

The various tests that can be used to study the ventilatory function can be roughly divided into two categories: qualitative and quantitative test methods. The qualitative test methods (e.g. Valsalva's manoeuvre,[37,38] Toynbee's manoeuvre,[39,40] sonotubometry,[41] and endoscopy[42]) only determine whether the Eustachian tube is patent or not. The quantitative test methods, such as the forced response test[43,44] and the pressure equilibration test,[45-48] have been used to actually measure Eustachian tube function. Zöllner[49] was the first to describe a method to quantify Eustachian tube patency by measuring the nasopharyngeal pressure needed to open the Eustachian tube during swallowing. He named his method the "Tubenwiderstandsmessung". This test was later modified to become the forced response test.[43] The forced response test is used to assess the forces that keep the Eustachian tube closed at rest (i.e. closing forces). These closing forces can be divided into the extraluminal forces, i.e. the pressure exerted by the cartilage and other surrounding tissues, and the luminal forces, i.e. mucosal forces such as the solid-to-solid adhesion of the Eustachian tube walls.[43,44,50] The pressure equilibration test, also called the inflation-deflation test, was introduced by Flisberg et al.[45] in 1963. Since then, the test has been used and modified by many investigators.[46-48] With the pressure equilibration test the ability to equilibrate positive and negative pressures is determined. In contrast with the forced response test, the pressure equilibration test much more imitates the normal physiological conditions of the Eustachian tube and the middle ear.

Measurement of protective function

The protection of the middle ear cavity by the Eustachian tube against extreme nasopharyngeal pressure variations can be measured with the sniff test.[51,52] During sniffing a negative pressure is generated in the nasopharynx. The Eustachian tube should remain closed to protect the middle ear against this pressure. Passive opening of the Eustachian tube during sniffing implies poor Eustachian tube protective function.

Measurement of clearance function

The clearance function can be measured in vivo by injecting dye or contrast fluid into the middle ear and monitoring its subsequent clearance by the Eustachian tube.[53,54] The time between injection of the dye and the first appearance of the dye at the nasopharyngeal orifice of the Eustachian tube is recorded as the clearance time. In vitro, the ciliary beat frequency and the ciliary beat pattern can be measured using high speed video imaging or a photoelectric method.[54,55] In animals, the muscular clearance function can be assessed by electrically stimulating the tensor veli palatini muscle to simulate swallowing.[36,56]

Impairment of Eustachian tube function[A]

A disturbance of the Eustachian tube may affect its ventilatory, protective and/or clearance function. Impairment of the different Eustachian tube functions can result from different factors, either endogenous or exogenous.

Impairment of ventilatory function

Different studies showed that the Eustachian tube ventilatory function is impaired in children with otitis media with effusion (OME) or otitis-prone children compared to healthy children.[53,57] Impairment of ventilation may result from a defective opening mechanism (i.e. functional obstruction) or from anatomical obstruction of the Eustachian tube (i.e. mechanical obstruction).[23,58]

In children, opening failure of the Eustachian tube is very common.[44,46] A defective opening mechanism may be due to increased compliance of the Eustachian tube (i.e. a lack of stiffness or being too "floppy"), inadequate muscular function or a deficiency of Eustachian tube surfactant. If the Eustachian tube cartilage lacks stiffness, the lumen may not open in response to contraction of the tensor veli palatini muscle. This may be due to the smaller density of elastin in the Eustachian tube cartilage in children.[11] Failure of the opening mechanism may also be the result of an inefficient tensor veli palatini muscle contraction. This inefficient contraction may be related to the immaturity of the neuromuscular system or the different anatomy of the Eustachian tube in children.[3,9] The importance of the normal anatomy of the Eustachian tube and its surrounding structures for efficient Eustachian tube opening is once more illustrated by the high incidence of Eustachian tube opening failure in patients with cleft palate.[59,60] The opening failure is most likely the result of several

[A] Adapted from "A comprehensive model for the aetiology of otitis media with effusion" M Straetemans, N van Heerbeek, ELGM Tonnaer, et al. Medical Hypotheses 2001;57:784-791

anatomical defects of the Eustachian tube and the paratubal muscles in these patients.[7,11,61] Finally, a relative deficiency, a reduced production or an altered phospholipid composition of surface tension lowering substances in the Eustachian tube (e.g. due to inflammation of the mucosal lining or genetic predisposition) may impair Eustachian tube opening.[62,63]
Mechanical obstruction of the Eustachian tube may result from inflammation of the mucosal lining secondary to infection or allergy or from an enlarged adenoid.[64,65] In rare cases, the Eustachian tube may be obstructed by a tumour (e.g. cholesteatoma, nasopharyngeal carcinoma). An impaired ventilatory function may contribute to the development of a negative middle ear pressure.[66]

Impairment of protective function
A loss of protective function of the Eustachian tube can be the consequence of an abnormally open Eustachian tube or a relatively short Eustachian tube.[23] In some cases, the Eustachian tube may be permanently or intermittently open, while in others the Eustachian tube is closed but has very low resistance. The Eustachian tube can also be relatively short, like in young children or even more in children with cleft palate or Down's syndrome.[9] In all these cases, nasopharyngeal secretions and micro-organisms may easily reflux into the middle ear. In addition, the middle ear is insufficiently protected against extreme nasopharyngeal pressure variations. In combination with habitual sniffing, this may be involved in the development of a persistent negative middle ear pressure.[67]
The local immunological defence mechanisms of the Eustachian tube can also be or become impaired. The secretion of secretory IgA may be impaired in some children, thus affecting the local immunological protective function.[68] An impaired chemotaxis of polymorphonuclear leukocytes may also affect the protection against invading pathogens.[69] In addition, the frequency of specific surfactant protein A haplotypes and genotypes were found to be different between children with recurrent otitis media compared with controls.[63] Such differences may affect the local defence by surfactant protein A.

Impairment of clearance function
Impairment of the mucociliary clearance function can be induced by viruses or bacteria and their endotoxins.[70-72] The inflammation that is induced by these micro-organisms causes major changes in the Eustachian tube mucosa including degeneration of ciliated cells. This results in impairment of the mucociliary clearance. Other causes of mucociliary dysfunction are primary ciliary

dyskinesia, cystic fibrosis, allergy, environmental pollutants and irradiation.[33,73-75] An impaired mucociliary clearance may facilitate bacterial penetration from the nasopharynx into the middle ear.[13,76] The muscular clearance function is most likely to be impaired when the muscular opening function of the Eustachian tube is inadequate.[77] In addition, clearance of fluid by muscle activity appeared to be impaired as a result of a high negative middle ear pressure.[56]

Summarising, impairment of the Eustachian tube functions may contribute to the development of persistent negative middle ear pressure and/or facilitate the invasion of the middle ear by pathogens. Both, persistent negative middle ear pressure as well as the accumulation of pathogens in the middle ear are assumed to contribute to the development of middle ear diseases, especially OME. This role of Eustachian tube dysfunction in the development of OME is schematically presented in Figure 2.[78]

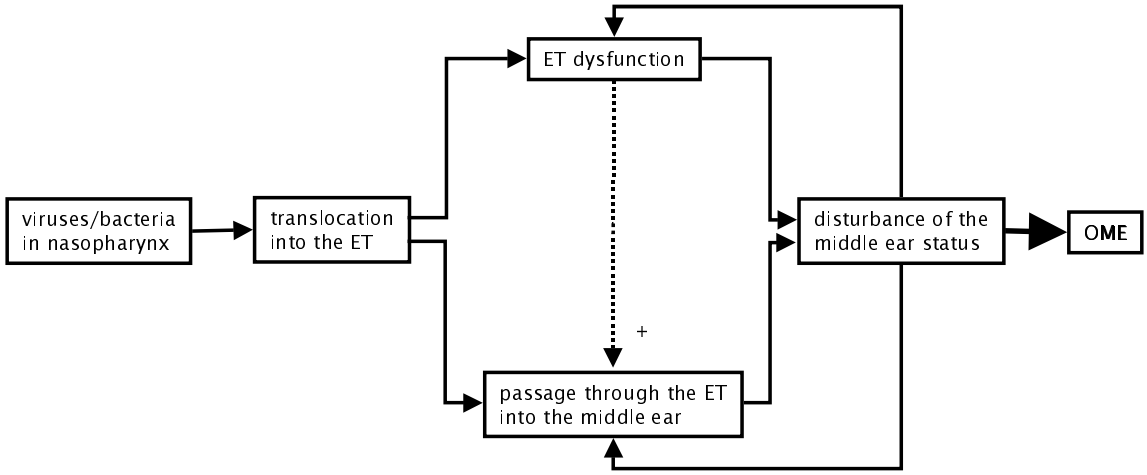

Figure 2. Schematic diagram of the role of Eustachian tube dysfunction in the development of OME.

The presence of bacteria or viruses in the nasopharynx is considered to be the first essential step in the aetiology of OME. These bacteria or viruses may be translocated into the Eustachian tube, where they can disturb the Eustachian tube function, or migrate through the Eustachian tube into the middle ear. An impaired Eustachian tube function may affect middle ear status by causing a negative middle ear pressure. Eustachian tube dysfunction may also facilitate the migration of pathogens through the Eustachian tube into the middle ear. Once in the middle ear, pathogens can affect the middle ear status by causing mucosal changes. In return, these disturbances of the middle ear status (i.e. negative

middle ear pressure, accumulation of pathogens, mucosal changes) may further impair the Eustachian tube function and/or facilitate the passage of pathogens through the Eustachian tube, thus creating an auto-amplifying loop.[56,70,79]
Persistent negative middle ear pressure may cause transudation of fluid or induce mucosal changes that lead to more mucus-producing cells in the middle ear.[80-82] Micro-organisms that have entered the middle ear may also induce mucosal cell differentiation leading to increased numbers of mucus-producing cells.[83] These changes bring about an increase in mucus secretion. If the immune system fails to eliminate the bacteria or viruses and the mucus is not adequately cleared by the Eustachian tube due to Eustachian tube dysfunction, mucus will accumulate and OME will develop.

Objectives

As described before, several tests have been developed and applied to study the Eustachian tube function in research and clinical settings. However, only little information is available concerning the validity and reliability of these tests. The question, therefore, remains whether it is possible to measure Eustachian tube function in children. To be able to measure Eustachian tube function in children, for instance to investigate the effect of medical intervention, a test is needed that meets the following criteria. Such a test should be:

-valid, i.e. the test should measure what it purports to measure
-reliable, i.e. the test should provide reproducible results
-safe
-user and patient-friendly

The forced response test and pressure equilibration test are widely used. Both tests are safe and user as well as patient-friendly. Unfortunately, validity of these tests cannot be established due to the lack of a “gold standard”. An important prerequisite for validity is, however, reliability. Reliability can be determined by repeatedly measuring the Eustachian tube function in the same child.
Regarding the applicability of these tests in epidemiological studies and clinical trials, it is important to know whether one or both ears of one child should be measured to characterise the Eustachian tube function of that child.

The desire to measure the Eustachian tube function in children led to the first objective of this thesis:
-to study the measurement conditions (i.e. type and number of tests, unilateral or bilateral measurement) that are necessary to obtain a reliable measure of the Eustachian tube function.

As shown in Figure 2, Eustachian tube dysfunction is assumed to contribute to the development of OME. It is, therefore, interesting to know whether the Eustachian tube functions can be affected in a positive way. If certain drugs or surgical interventions improve the Eustachian tube function, they may be effective to prevent or treat OME as well. However, the question remains which interventions are effective to improve the Eustachian tube function.
At present, the insertion of ventilation tubes is the most commonly performed intervention in children with persistent OME. Ventilation tubes temporarily replace the function of the Eustachian tube. They resolve the effusion and provide aeration of the middle ear, thus restoring normal hearing. However, besides being a substitute for Eustachian tube function, the insertion of ventilation tubes may affect Eustachian tube function as well.
Nasal decongestants are also commonly used in children with persistent OME, based on the assumption that they improve the Eustachian tube function. However, the knowledge about the effect of topical decongestants on the Eustachian tube function is limited.
Since surfactant is assumed to be an important factor for normal functioning of the Eustachian tube, the administration of exogenous surfactant is suggested to improve Eustachian tube function. As described before, a relative deficiency or a reduced production may impair the Eustachian tube functions.

The desire to determine which interventions are effective to improve the Eustachian tube function led to the second objective of this thesis:
-to study the effect of common (e.g. ventilation tubes, nasal decongestants) and promising (e.g. surfactant) interventions on the Eustachian tube function.

Outline of this thesis

In *Chapter 2*, the reliability of the forced response test and pressure equilibration test, the tests that are most widely used, is outlined. In addition, the differences in function between the left and right Eustachian tube in children with bilateral OME are described in *Chapter 3*.
A comprehensive summary of the results of all studies that investigate the therapeutic improvement of the Eustachian tube function is given in *Chapter 4*. In *Chapter 5*, the effect of ventilation tubes on Eustachian tube ventilatory function in children is described. The effect of a topical decongestant on Eustachian tube ventilatory and protective function in children with ventilation tubes is presented and discussed in *Chapter 6*. In *Chapter 7*, the effect of

surfactant on the Eustachian tube ventilatory and clearance function in rats is described.

Finally, the overall conclusions of this thesis are discussed in the light of the present knowledge of Eustachian tube (dys)function in *Chapter 8*. Some practical implications and proposals for future research are suggested.

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Chapter 2

Reliability of manometric Eustachian tube function tests in children

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Abstract

Objective: To assess the reliability of manometric Eustachian tube (ET) function tests in children with ventilation tubes in situ.

Study design: Repeated manometric ET function tests during one session.

Setting: The study took place at a secondary referral hospital and at a tertiary referral hospital.

Patients: Ninety-nine children with ventilation tubes in situ because of persistent otitis media with effusion.

Main outcome measures: Opening pressure (Po), closing pressure (Pc), and tubal function group.

Results: Analysis of Po and Pc showed a decrease with repeated measurement ($p=0.0001$ and $p=0.001$, respectively). The effect of repeated measurement on Po was more pronounced than the effect on Pc. The results of the first and second pressure equilibration tests showed 99% agreement.

Conclusions: This study showed good reproducibility of the categorised results of the pressure equilibration test, whereas the results of the forced response test seemed to be less reproducible and showed a downward shift with repeated measurement. A single measurement using wet swallowing and starting pressures of 100 and -100 daPa and the mean of the first three measurements of the Po and Pc are sufficient to determine ET function. Further studies are needed to determine the discriminative power of these tests in children with different degrees of middle ear disease.

Introduction

Otitis media with effusion (OME) is very frequent during childhood.[1] In most cases OME is a self-limiting disease, in some, however, the effusion persists. Because persistent OME can cause long-standing hearing loss with possible adverse effects on speech and language development,[2] treatment of OME is indicated in patients with persistent OME. Several treatment strategies (e.g. antibiotic treatment, myringotomy with and without insertion of ventilation tubes, and adenoidectomy) have been advocated.[3] Of all the surgical treatments for OME, the insertion of ventilation tubes is performed most often, and it has become one of the most common operations in young children.[4,5] Ventilation tubes usually eliminate the effusion and restore hearing. However, ventilation tubes do not cure OME; they treat the symptoms instead of the cause. Several factors have been and still are reported as causal for OME.[6-9] Eustachian tube (ET) dysfunction is assumed to be one of these causal factors, especially in children. ET function in children has been studied by several authors.[6,10-15] Different ET function tests were used in these studies, including Valsalva's manoeuvre, tympanometry and manometric tests (i.e. forced response test and pressure equilibration test). Other techniques described to evaluate ET function are radiographic tests,[16] phototubometry,[17] and endoscopy.[18] The forced response test and the pressure equilibration test are most widely used. Both tests are generally accepted and easy to perform. However, little is known about the reliability of these tests.[19,20] The aim of this study was to assess the reliability of manometric ET function tests in children with ventilation tubes in situ.

Patients and Methods

The study population consisted of 99 children (48 boys and 51 girls) with a mean age of 5.7 years (range: 1.7-12.1 years), who had received ventilation tubes because of persistent OME. A total of 144 ears were examined (69 right ears and 75 left ears). In 45 out of the 99 children, the tests were performed on both ears. Manometric ET function tests were performed repeatedly as described later by the same examiner. Children with syndromes that may affect the middle ear (e.g. Down's syndrome, cleft palate) were excluded. Parental consent was obtained in all cases.

Equipment

A recently calibrated TYMP87 middle ear analyser (Rexton Danplex A/S, Copenhagen, Denmark) was used for the measurements. Pressure applied by the pump ranged from 600 daPa to -600 daPa, at a pump rate of 50 daPa/s.

Procedure

The patient was seated comfortably and given instructions. The presence and permeability of the ventilation tube were confirmed otoscopically. The external ear canal was then sealed airtight with the probe of the middle ear analyser. Before the measurements, a test was performed to check whether there was any leakage. Subsequently, passive ET function was assessed repeatedly by measuring the opening pressure (Po) and the closing pressure (Pc; forced response test). In addition, the ability to equilibrate positive and negative pressures (pressure equilibration test) was assessed. The ability to equilibrate pressure was used to express the muscular opening function of the ET (i.e. active ET function). The pressure in the ear canal and middle ear was recorded continuously during both tests. Because opening of the ET before the forced response test may have an effect on the results of the test,[20,21] we performed the forced response test first, followed by the pressure equilibration test in all patients.

Forced response test

The Po and Pc were assessed by increasing the pressure in the middle ear until the ET opened spontaneously. This passive opening of the ET was indicated by a sudden decrease in the pressure, as shown in Figure 1. The maximum pressure was recorded as the Po. Immediately after opening of the ET, the pump was turned off and the ET closed spontaneously. The Pc was the residual pressure after passive opening of the ET. Patients were asked to avoid swallowing during the forced response test. The forced response test was performed five times in a row within 3 minutes to assess the reproducibility of the test.

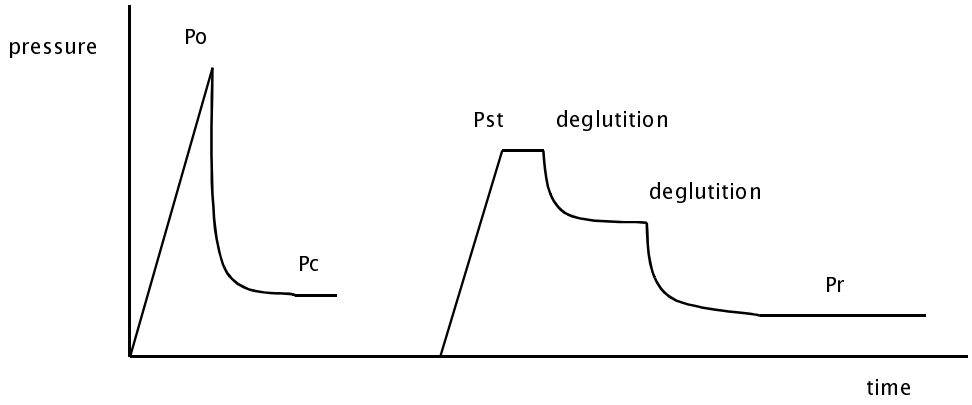

Figure 1. Examples of a recording of the forced response test [left] with opening (Po) and closing pressure (Pc), and the pressure equilibration test [right] with starting (Pst) and residual pressure (Pr).

Pressure equilibration test

To assess the patients' ability to equilibrate pressure, positive and negative pressures (starting pressures) were applied to the middle ear. The patient was then asked to swallow some lemonade every 5 to 10 seconds. Opening of the ET was recorded as a sudden change in the pressure, as shown in Figure 1. The test was continued until equilibration was complete or until the residual pressure (Pr) had remained stable during five consecutive deglutitions. The Pr and the total number of deglutitions were recorded. The pressure equilibration test was performed twice within 3 minutes to assess the reproducibility of the test. Both measurements were performed with starting pressures of 200 and -200 daPa. In some patients, a starting pressure of 200 daPa could not be applied because the ET opened spontaneously before 200 daPa had been reached. In these patients both tests were performed with starting pressures of 100 and -100 daPa instead of 200 and -200 daPa.

In most ears, in which starting pressures of 200 and -200 daPa could be used, a third measurement was performed with starting pressures of 100 and -100 daPa to assess the effect of a different starting pressure on active ET function.

The results of the pressure equilibration tests of each patient were classified into four tubal function groups according to Elner et al.[22] The patients in group I were able to equilibrate the positive and negative pressures completely (Pr<10 daPa and >-10 daPa, respectively). Group II patients were able to equilibrate the positive and negative pressures partially (Pr>10 daPa or <-10 daPa, respectively). Group III patients were able to equilibrate the positive pressure completely or partially, but were unable to equilibrate the negative pressure. The patients in group IV were unable to equilibrate the positive and negative pressures.

Statistical analysis

Data were analysed by univariate and multivariate analysis using the SAS statistical package (SAS Institute, Cary, NC, USA). Differences in mean Po, Pc and Pr were tested using the Student's t-test. Po and Pc were analysed with order of measurement, sex, tubal function group, and age as covariables, using multiple linear regression analysis. Pr was not analysed by multivariate analysis because no differences were expected based on the results of the univariate analysis. The ears in tubal function groups I and II were not analysed, since these groups consisted of 0 and 3 ears, respectively.

Results

Forced response test

Figure 2 shows the mean Po and Pc (± standard deviation [SD]) of all five consecutive measurements. Both Po and Pc showed wide variance. The Po at the first measurement ranged from 136 to 600 daPa and the Pc ranged from 24 to 275 daPa. The second to fifth measurement showed comparable and, in some cases, even more profound variance in Po and Pc. Univariate analysis revealed that Po decreased significantly by 34 daPa (p=0.006) from 320±108 daPa at the first measurement to 286±103 daPa at the second measurement. The changes in Po during later measurements were not statistically significant, nor were the changes in Pc. Despite the gradual decrease in mean Po and Pc in the whole group shown in Figure 2, the course of repeated Po and Pc measurements showed considerable intraindividual variation. When the differences between the third and fourth Po and Pc were studied in all patients, mean differences (± intraindividual SD) of 7±40 daPa and 3±22 daPa were found for Po and Pc, respectively. Mean differences and intraindividual SDs between other pairs of measurements were within the same range.

Po and Pc were highly correlated (all correlation coefficients ≥0.73). Univariate analysis did not reveal any significant differences in Po and Pc between left and right ears, boys and girls, or different age groups.

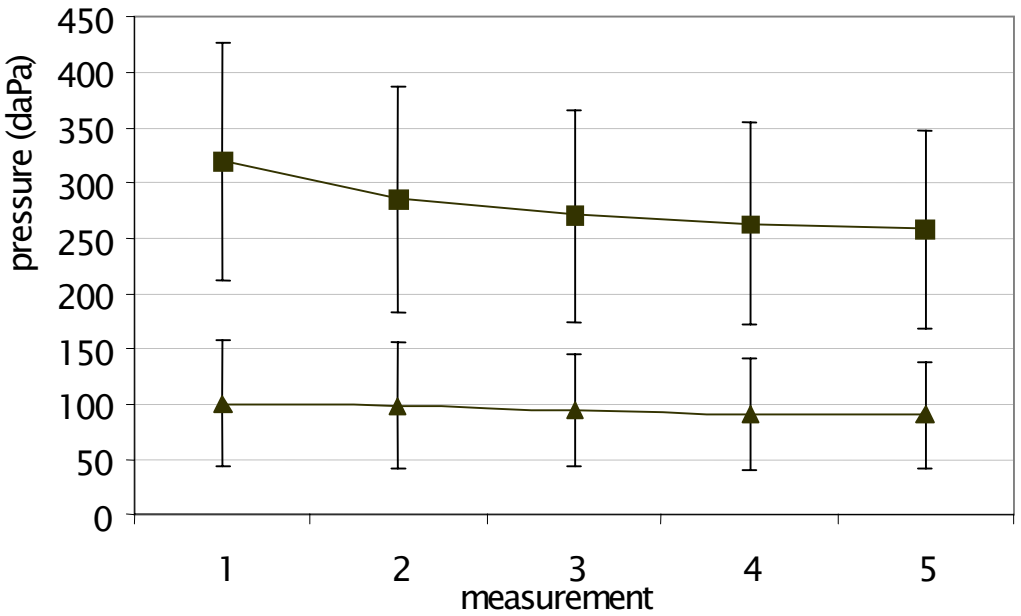

Figure 2. Mean forced opening pressure (solid square) and closing pressure (solid triangle) [± SD] of all five consecutive measurements in 144 ears.

Pressure equilibration test

Table 1 shows the results of the first and second pressure equilibration tests from all 144 ears. In 89 ears, 200 and -200 daPa were applied as starting pressures, and in 55 ears 100 and -100 daPa were applied as starting pressures. None of the children were able to equilibrate the positive and negative pressures completely (as required for classification into group I). Comparison of the results from the first and second tests in the whole group showed 99% agreement; two ears changed from group IV to group III. In addition, the Pr from the first and second tests in group III ears were highly correlated (correlation coefficient 0.83) and there was no significant difference between the first and second tests (p=0.39). The Pr from the left and right ears were also correlated (correlation coefficient 0.59).

Table 1. Results of the first and second pressure equilibration tests of all 144 ears.

		first test		
		group II	group III	group IV
second test	group II	3		
	group III		104	2
	group IV			35

Univariate analysis did not reveal any significant differences in Pr or tubal function group between left and right ears, boys and girls, or different age groups.

A third pressure equilibration test was performed on 84 of the 89 ears, in which 200 and -200 daPa were applied as starting pressures during the first and second measurements. A change in starting pressure from 200 daPa to 100 daPa had considerable influence on the outcome of the test. More than half of the group III ears deteriorated to group IV when starting pressures of 100 and -100 daPa were applied instead of 200 and -200 daPa. The group IV ears and the only group II ear in the second test remained in the same tubal function groups.

When the results of the forced response test were compared with the results of the first pressure equilibration test, Po proved to be significantly higher in group IV ears than in group III ears. Mean Po (±SD) from all five measurements was 266±79 daPa in group III ears and 321±111 daPa in group IV ears (p=0.008). The mean Pc also tended to be higher in group IV ears, but multivariate analysis did not show any significant difference.

Multivariate analysis

Multiple linear regression analysis showed a statistically significant association of Po with order of measurement (p=0.0001) and active tubal function group (p=0.0005), whereas Pc was associated only with order of measurement (p=0.001). Po and Pc both decreased at each following measurement. However, the effect of repeated measurement on Po was more pronounced than the effect on Pc, as depicted in Figure 2. Po was found to be higher in group IV ears than in group III ears. No difference in Pc was found between group III and group IV ears. Po and Pc were not found to be associated with age or sex.

Discussion

This study showed good reproducibility of the results of the pressure equilibration test in children with OME. The results of the forced response test, however, seemed to be less reproducible and showed a downward shift with repeated measurement. Because of the lack of a gold standard for measuring ET function, we still do not know whether the results of the tests reflect real ET function. However, the close associations between the different tests suggest that they do reflect relevant aspects of ET function.

Repeated measurements of Po and Pc resulted in decreasing values of Po and Pc. This observation is in agreement with those found in other studies.[20,21,23] Po is assumed to reflect the total closing forces (i.e. luminal and extraluminal forces) of the ET. Pc is assumed to represent the extraluminal forces (e.g. pressure of the cartilage and other surrounding tissues) and the difference between Po and Pc is assumed to represent the luminal forces (e.g. mucosal factors, surface tension, viscosity of secretion).[12,21,24,25] Apparently, repeated forced response measurement diminishes the luminal and extraluminal factors. Figure 2 shows that the effect on the luminal forces (Po minus Pc) was more pronounced than the effect on the extraluminal forces (Pc). Possibly the presence of surfactant and secretions changed as a result of the passage of air through the ET, resulting in smaller luminal forces. The pressure of the cartilage and other surrounding tissues may have been changed as a result of repetitive opening of the ET, resulting in smaller extraluminal forces. This decrease in total closing forces suggests that the closing forces of the ET at rest are probably best reflected by the first measurement. Despite the downward shift in mean Po and Pc in the whole group, considerable intraindividual variability was observed. This finding was probably caused by fluctuation in muscular activity during the measurements, similar to the fluctuation found in rats by Mulder.[26] This

intraindividual variability indicates that single measurements of Po and Pc are insufficiently reliable.

The desire to retain the results of the first measurement versus the necessity to use the results of more than one measurement constitutes a trade-off between validity and precision. We suggest a pragmatical solution: take the mean of the first three measurements to characterise each individual.

Another question regarding the forced response test is whether the test is responsive to middle ear conditions and discriminative in children with various degrees of middle ear effusion. Bylander et al.[12] studied Po and Pc in otologically healthy children of different ages. They found means and SDs of Po and Pc comparable with those found in this study. Stenström et al.[6] compared Po and Pc in otitis-prone children (n=50) and otologically healthy children (n=49) and did not find any overall differences in mean Po and Pc. Cantekin et al.[21] compared children with OME (n=137) with children with traumatic perforations (n=29) and did not observe any differences. The resemblance of the distributions of Po and Pc in children with OME and otologically healthy children is unexpected because ET function is assumed to play a role in the pathogenesis of OME. This also raises doubt about the discriminative power of the forced response test.

Our results from the pressure equilibration test, classified into four tubal function groups, showed good reproducibility, as did the results reported by Groth et al.[20] Others found considerable test-retest variability in children with OME, but in these studies the time interval between the tests was considerably longer.[19,23] We suggest that active ET function is a dynamic quality that fluctuates around an individual average.

During active opening of the ET, the patient has to overcome the closing forces. Probably the positive starting pressure helps at opening the ET by partially compensating for the closing forces. Therefore, the use of a lower positive starting pressure (100 instead of 200 daPa) may result in poorer opening of the ET. However, as long as the same starting pressures are used within an individual, the reproducibility of the results is good, as described previously.

Several authors found that the method of equilibration (e.g. wet or dry swallowing, yawning) influenced the results of the pressure equilibration test.[10,24] However, there is no reason to assume that the method of equilibration has an effect on the reliability of the test. In our opinion, it is difficult to achieve a situation in which children, especially young children, use dry swallowing or the method of free choice (i.e. open the mouth, yawn, move the mandible and swallow repeatedly). Therefore, we did not use methods of equilibration other than wet swallowing (i.e. swallowing water, lemonade, or orange juice).

Based on the results of the current study, a single measurement from the pressure equilibration test using wet swallowing is sufficient to characterise individuals. We recommend using starting pressures of 100 and -100 daPa because a substantial proportion of ears tend to open passively if a higher positive starting pressure is applied.

In this study, almost all the children had tubal function group III or IV. This finding questions the discriminative power of the subdivision of the results into four categories in children with OME. However, others found that subdivision into categories was useful to discriminate between children with OME and otologically healthy children.[6,21]

Conclusions

The pressure equilibration test seems more useful than the forced response test. However, further studies are needed to elucidate the discriminative power of the forced response test and to determine whether the pressure equilibration test and the subdivision of the results into four categories is useful to compare children with different degrees of middle ear disease. These studies have already been started at our institute. We recommend taking the mean of the first three measurements of Po and Pc to determine passive ET function. When active ET function is determined, a single measurement using wet swallowing and starting pressures of 100 and -100 daPa is sufficient.

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Chapter 3

Left-right differences in Eustachian tube function in children with ventilation tubes

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KJAO Ingels
GA Zielhuis

Abstract

Objectives: To study the intraindividual variation in Eustachian tube (ET) function in children with ventilation tubes.

Study Design: Prospective comparative study.

Methods: The forced response test, the pressure equilibration test and the sniff test were performed on both ears of 148 children. The results of both ears were compared.

Results: No systematic differences were found between the left and the right ears. However, the intraindividual variation was very pronounced. The variation in opening and closing pressure (forced response test) within children was of similar magnitude as the variation in opening and closing pressure between children. Twenty-eight percent of the children had different active ventilatory function (pressure equilibration test) in both ears and 15% had an opposite result in each ear with respect to the sniff test.

Conclusions: This study shows that ET function is much more a characteristic of the individual ear than of the individual child. These findings also question the validity of trials on ET function or middle ear disease that use the opposite ear as a control (split level design).

Introduction

Otitis media with effusion (OME) is characterised by the accumulation of viscous fluid in the middle ear cavity behind an intact tympanic membrane, without the signs and symptoms of an acute infection (such as otalgia, fever, and a red tympanic membrane that is full or bulging).[1] OME is highly prevalent among young children, with peak prevalences at around one and five years of age.[2,3] The aetiology of OME is still only partly understood. It is considered to be a multi-factorial disease process with a variety of etiological factors.[4] Eustachian tube (ET) dysfunction as well as an aberrant immune response are both assumed to play an important role in the development, persistence and recurrence of OME and other middle ear diseases.[5-10]

Until now, it remains unknown whether OME develops independently in each ear or must be regarded as one disease with manifestations in both ears at the same time. Johnson et al.[11] collected effusions from 64 children with bilateral OME. The concentrations of three cytokines, the rheological properties and the biochemical composition of the pairs of effusions were measured. They found significant differences for several parameters, suggesting that each ear undergoes pathological changes independently. In line with these findings, the left and right ET may also show differences in function. Previously, we reported that univariate analysis did not reveal any significant differences in opening pressure, closing pressure or tubal function group between the left and right ET.[12] However, as looking for asymmetry was not the primary aim in this study and the right ear was systematically measured first, bias may have occurred.

The aim of this study is to describe the differences in ET function between left and right in children with OME by comparing the results of the forced response test (passive ventilatory function), the pressure equilibration test (active ventilatory function) and the sniff test (protective function). A potential difference between left and right is relevant for further understanding of the aetiology of OME and for the analysis and interpretation of clinical trials that use the opposite ear as a control.

Patients and Methods

The study enclosed two populations of children, who were recruited from six primary schools (population 1) and six hospitals (population 2). All the children had been treated with ventilation tubes due to persistent, bilateral OME. Children with syndromes that may affect the middle ear (e.g. Down's syndrome, cleft palate) were excluded. The children in population 2 visited the outpatient department of one of the hospitals only because they participated in a larger

study investigating the etiological factors of recurrent OME. Both ears of each child were examined. In population 1, random numbers were used to determine the sequence in which both ears were measured, i.e. the measurement sequence. In population 2, the right ears were systematically measured first. The forced response test, the pressure equilibration test and the sniff test were performed as described later. The measurements were performed by two investigators and took place in a tranquil room. Parental consent was obtained in all cases.

Equipment

The same TYMP87 middle ear analyser (Rexton Danplex A/S, Copenhagen, Denmark) was used for all measurements. The pressure in the middle ear was measured continuously during all the tests. Pressure applied by the pump ranged from 600 to -600 daPa, at a pump rate of 50 daPa/s.

Procedure

The child was seated comfortably and instructions were given. The permeability of the ventilation tubes was assured by tympanometry and otoscopy and the external ear canal was sealed airtight with the probe of the middle ear analyser.

First, the forced response test was performed to measure the passive opening and closing pressure (Po and Pc, respectively) of the ET. The Po was assessed by increasing the pressure in the middle ear until the Eustachian tube opened spontaneously. This passive opening of the ET was indicated by a sudden decrease in the pressure. The maximum pressure was recorded as the Po. Immediately after opening of the ET, the pump was turned off and the ET closed spontaneously. The Pc was the residual pressure after passive closure of the ET. Children were asked not to swallow during the forced response test. Since the results of the forced response test show a downward shift with repeated measurements, the Po and Pc were recorded three times and the means of the three Po and Pc were used for analysis.[12]

Subsequently, the pressure equilibration test was performed. This test measured the children's ability to equilibrate positive and negative pressures. Positive and negative pressures of 100 and -100 daPa respectively were applied to the middle ear and the effect of repetitive deglutitions (the child was asked to swallow some water) on these pressures was recorded. Opening of the ET was recorded as a sudden change in the pressure. The test was continued until equilibration was complete or until the residual pressure (Pr) had remained stable during five consecutive deglutitions. The Pr after these deglutitions was recorded. Based on

the Pr each subject was classified into one of four tubal function groups according to Elner et al.[13] The patients in group I were able to equilibrate the positive and negative pressures completely (Pr<10 daPa and >-10 daPa, respectively). Group II patients could equilibrate the positive and negative pressures partially (Pr>10 daPa and <-10 daPa, respectively). Group III patients could equilibrate the positive pressure completely or partially, but were unable to equilibrate the negative pressure. The patients in group IV were unable to equilibrate the positive and negative pressures.
Finally, the sniff test was performed to assess the children's ability to produce a negative pressure in the middle ear by sniffing forcefully. Each child was asked to sniff five times. If the child could create a negative pressure in the middle ear, the sniff test was considered as positive, if not, the sniff test outcome was negative.

Statistical analysis
Data were analysed with the statistical package SPSS. The mean difference between Po_{left} and Po_{right} and between Pc_{left} and Pc_{right} were tested using the paired t-test, with standard deviations and 95% confidence intervals. Left-right differences in tubal function group and sniff test were shown in crosstables, described and tested using the McNemar test for paired observations.

Results
In population 1, in which a random measurement sequence was used, no differences were found in Po, Pc, tubal function group or sniff test results between the ears that were measured first and the ears that were measured next (all p-values>0.4). This confirmed the results of a previous study, that found no effect of the measurement sequence on Po and Pc.[5] Apparently, the measurement sequence does not affect the outcome of the test. For that reason, and because both populations were similar with regard to age and sex distribution, the results of both populations were pooled to study the intraindividual differences in ET function. The total population consisted of 148 children, 72 boys and 76 girls, with a mean age of 5.0 years (range: 2-9 years).

Forced response test
In Table 1, the results of the forced response test are presented. No systematic differences between Po_{left} and Po_{right} and between Pc_{left} and Pc_{right} were found (mean difference 7 daPa, (95% CI: -7 – 21 daPa), and 0 daPa, (95% CI: -9 – 8 daPa), respectively). As the observations of the Pc were not normally distributed, a

Wilcoxon signed rank test and a paired t-test after ln-transformation of the mean Pc_{left} and Pc_{right} were performed as well, leading to similar results (both p-values=0.9). However, the distribution of the individual differences between Po_{left} and Po_{right} and between Pc_{left} and Pc_{right} showed a very wide range and considerable irregularity, as shown in Figures 1 and 2. The differences between Po_{left} and Po_{right} ranged from -200 to 275 daPa with a SD of 86 daPa and the differences between Pc_{left} and Pc_{right} ranged from -180 to 180 daPa with a SD of 53 daPa. The standard deviations of the mean Po and mean Pc of all the ears, indicating the interindividual differences in Po and Pc, were of the same magnitude (approximately 95 daPa for Po and around 50 daPa for Pc, Table 1). Apparently, the variation in Po and Pc within one child was almost equal to the variation in Po and Pc between different children. The left and right ears were not completely independent, because the correlation coefficient between left and right ear was 0.58 for Po and 0.44 for Pc.

Table 1. Mean opening and closing pressures of the left and right ears and mean differences between left and right, with corresponding standard deviations. (n=148)

	Po_{left}	Po_{right}	Pc_{left}	Pc_{right}
mean (daPa)	311	318	95	95
SD (daPa)	90	98	52	49
mean difference (daPa) (95% CI)	7 (-7 – 21)		0 (-9 – 8)	
SD of the difference (daPa)	86		53	

Po: opening pressure; Pc: closing pressure; SD: standard deviation.

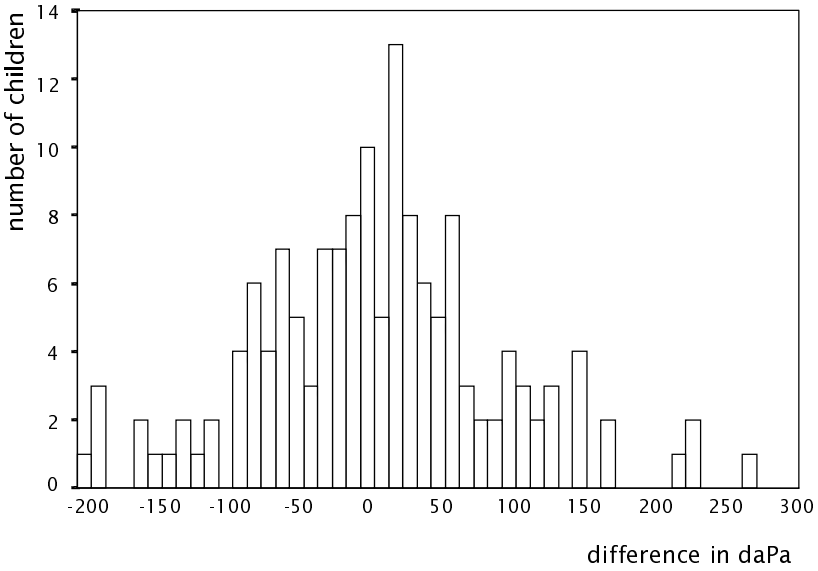

Figure 1. Distribution of the individual differences between left and right opening pressure. (n=148)

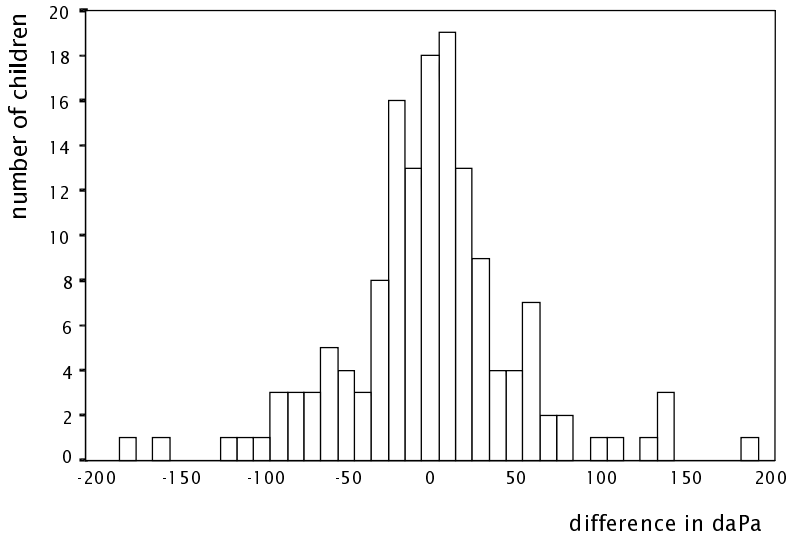

Figure 2. Distribution of the individual differences between left and right closing pressure. (n=148)

Pressure equilibration test

In Table 2, the tubal function groups of the left and the right ears are compared. In seven children the pressure equilibration test could not be performed due to poor co-operation of the child. Poor active ventilatory function, i.e. tubal function group III or IV, was found in 94% of all ears. Most children had the same tubal function group in both ears and no systematic difference was found between left and right ($p>0.2$). Nevertheless, a substantial proportion of children (28%) had a different tubal function group in the left and right ear, showing considerable intraindividual variation in active ventilatory function in these children.

Table 2. Tubal function group of the left and the right ear of each child. (n=141)

		Left ear			
		group I	group II	group III	group IV
Right ear	group I	-	-	-	-
	group II	1	3	2	1
	group III	-	3	22	20
	group IV	1	1	11	76

Sniff test

Table 3 shows the results of the sniff test. Thirty-five children were not able to perform the sniff test. The majority of the remaining 113 children had the same result in both ears, so no systematic difference was found between left and right

(p=0.6). However, 17 children (15%) were found to have a different outcome in both ears, illustrating intraindividual variation in protective ET function as well.

Table 3. Results of the sniff test of the left and right ear of each child. (n=113)

		Left ear	
		positive	negative
Right ear	positive	14	10
	negative	7	82

Discussion

No systematic differences in ventilatory and protective ET function were found between the left and the right ear in children with OME. However, the intraindividual variation was large. The variation in Po and Pc within children was of similar magnitude as the variation in Po and Pc between children. Twenty-eight percent of the children had different active ventilatory function (i.e. different tubal function groups) in both ears and 15% had an opposite result in each ear with respect to the sniff test. These results suggest, that the left and right ET of one child can have a very different function and that the ET function of one ear does not predict the ET function of the opposite ear.

These intraindividual differences can not simply be explained by inaccuracy of the test methods, because the mean of the first three measurements of each ear were used to obtain reproducible values of Po and Pc, and because the reproducibility of the results of the pressure equilibration test is almost 100%.[12] Although a considerable test-retest variability in the results of the sniff test was found by others,[14,15] their results do not indisputably indicate inaccuracy of the sniff test, because long time intervals between the tests were used in these studies. While measurement error thus is an unlikely explanation, the cause for the intraindividual variation remains unclear. The variation in ET function may be explained by anatomical or morphological differences, either congenital or acquired. Another explanation may be the existence of alternating mucosal congestion of the left and right ET, comparable to the nasal cycle.[16]

The overall prevalence of OME is approximately 30%. In 60% of these cases the effusion is bilateral, but in the other 40% the effusion is unilateral.[2,3] Other middle ear diseases that are believed to be associated with ET dysfunction, such as acute otitis media and retraction of the tympanic membrane, frequently occur unilateral as well.[7,17,18] Apparently, local factors, such as ET dysfunction, play an important role in the development of OME and other middle ear diseases, because otherwise these diseases would only manifest bilaterally. Our

population consisted of children with bilateral OME, but a substantial proportion was found to have different ET function on each side. This suggests, that ET function is much more a characteristic of the individual ear than of the individual child and thus contributes independently to the development of the OME in the corresponding ear. According to this, a very pronounced difference in ET function between left and right, may result in the unilateral occurrence of middle ear disease.

The findings of this study also have important implications for clinical trials on ET function that use the opposite ear as a control (split level design). The assumption that the untreated ear serves as a good reference for the opposite ear in such studies is not substantiated by the data of our study. On the contrary, there can be a wide difference between the left and right ear of one child.

Conclusions

The ET function of the left and right ear were found to be different in many children with bilateral OME, indicating that ET function is much more a characteristic of the individual ear than of the individual child. ET dysfunction seems to be a local process to a large extent and probably contributes independently to the development of OME in the corresponding ear. The specific relation and balance between local and systemic factors in the aetiology of OME yet remain to be investigated. The results of this study also question the validity of trials on ET function or middle ear disease that use the opposite ear as a control (split level design).

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Chapter 4

Therapeutic improvement of the Eustachian tube function: a review

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Abstract

An impaired Eustachian tube (ET) function is assumed to be an important factor in the pathogenesis of different middle ear diseases. Therefore, several investigators have studied different treatment strategies to improve ET function. The aim of this review is to provide a comprehensive summary of the results of these studies on therapeutic improvement of ET function. The English language literature was searched systematically to identify all articles that described the effect of different interventions on ET function. Although the results were not uniform throughout the different studies and despite several restrictions of the reviewed studies, the results of this review indicate that the ET function may be improved by medical intervention. However, it seems premature to recommend any of the interventions reviewed in this paper to improve ET function in humans. More studies, preferably randomised, placebo-controlled trials, should be conducted to assess the efficacy of different interventions on ET function.

Introduction

The Eustachian tube (ET) was named after Bartholomeus Eustachius who gave a detailed description of the ET in his "Epistola de auditus organis" in the sixteenth century.[1] In the twentieth century the importance of the ET with respect to ventilation, protection and clearance of the middle ear was recognised. Frequent active opening of the ET allows ventilation of the middle ear cavity, thus preventing the development of a negative middle ear pressure. The normally closed ET protects the middle ear from ascending secretions and micro-organisms as well as from nasopharyngeal pressure variations. The mucosal lining of the ET, with its mucociliary epithelium, is involved in local defence against pathogens and is concerned with clearance of secretions and debris from the middle ear towards the nasopharynx.[2] The clearance function of the ET is a complex mechanism that depends on many factors like ciliary activity, fluid characteristics and gravity.

The ventilatory, the protective and the clearance function of the ET can be disturbed by endogenous or exogenous conditions, for example, cleft palate,[3] allergy[4] or upper respiratory tract infection.[5] An impaired middle ear ventilation can cause a persistent negative middle ear pressure.[6] In case of an impaired protective function, habitual sniffing may cause a persistent negative middle ear pressure as well.[7] Poor protective function of the ET can also facilitate the entrance of bacteria into the middle ear. Disturbances of the mucociliary defence mechanism may result in the accumulation of secretions and can facilitate bacterial invasion and subsequent infection. Both persistent negative middle ear pressure and accumulation of pathogens and secretions in the middle ear are assumed to contribute to the development of acute otitis media, chronic otitis media and especially otitis media with effusion (OME).

The assumption that an impaired ET function may be an important factor in the pathogenesis of different middle ear diseases has incited several investigators to study different treatment strategies to improve ET function. Therapeutic improvement of the ET function may prevent the development of a negative middle ear pressure or the accumulation of pathogens in the middle ear. These treatment strategies may also be effective to prevent, or resolve, the subsequent middle ear diseases. The aim of this review is to provide a comprehensive summary of the results of the studies on therapeutic improvement of ET function.

Methods

A survey was made of the English language literature since 1966. The Medline and Pubmed databases were searched systematically to identify all articles that described the effect of drugs, surgery or other interventions on ET function. Subsequently, articles were selected based on study population, intervention and test methods. Finally, all selected articles were thoroughly evaluated.
Articles that studied the effect on the ET function in patients with cleft palate or patulous ET were excluded from further review. Interventions that caused an impairment of the ET function, such as certain inflammatory mediators and surgical lesion of the tensor veli palatine muscle, were also excluded.

Test methods

ET ventilatory function can be assessed in several ways: manometric tests (i.e. forced response test and pressure equilibration test),[8] perfusion pressure test,[9] Valsalva's manoeuvre[10] and sonotubometry.[11] The forced response test is used to assess passive ET function by measuring the opening pressure (Po) and the closing pressure (Pc). A decrease of the Po or the Pc is generally considered to reflect an improvement of the ET. Active ET function is assessed by measuring the ability to equilibrate applied positive and negative pressures by swallowing repetitively (pressure equilibration test). Both tests are usually performed on ears with a non-intact tympanic membrane (e.g. with a perforation or a ventilation tube in situ). Pressure can be directly applied to the middle ear through this opening in the tympanic membrane.[8] The tests can also be performed, when the tympanic membrane is intact. In those cases, a pressure chamber is used to apply pressure to the middle ear.[12] Another method, that is similar to the forced response test, is the perfusion pressure test. This test measures the pressure necessary to keep a constant flow of air or fluid passing through the ET (i.e. perfusion pressure). Measurement of the middle ear pressure by tympanometry, during performance of Valsalva's manoeuvre, can also be used to assess opening of the ET. An increase of the middle ear pressure during the manoeuvre indicates opening of the ET.[10] Sonotubometry is based on the passage of sound through the ET. When the ET opens (e.g. during swallowing) the sound pressure level increases.[11]
The protection of the ET against extreme nasopharyngeal pressure variations can be measured with the sniff test. By sniffing forcefully, a negative nasopharyngeal pressure is generated. Normally, the ET remains closed during minor pressure variations in the nasopharynx. However, in some subjects, the ET opens passively during sniffing, resulting in a negative middle ear pressure. This

negative middle ear pressure can be measured tympanometrically.[7] This indicates poor protection of the middle ear by the ET.
Clearance function can be measured by injecting dye or contrast fluid into the middle ear and subsequent monitoring of the clearance through the ET.[13,14] The time between injection of the dye and the first appearance of the dye at the nasopharyngeal orifice of the ET is recorded (clearance time).
All these test methods are in use for assessment of the ET function and were included in the review. The middle ear pressure, that is measured tympanometrically, is also frequently used as a measure of the ET function. Although the ET is important in maintaining an ambient pressure in the middle ear, it is not the only factor involved. Changes in outcome of tympanometry are not necessarily related to changes of the ET function. Studies that used tympanometry as the only measure for ET function were, therefore, excluded.

Results

Most studies evaluated the effect of drugs or surgical intervention on the ventilatory function of the ET. Only a few studies reported the beneficial effect of drugs on protective or clearance function. There were no articles retrieved that studied the effect of alternative intervention strategies on ET function. Table 1 summarises all the studies that were included in the review. These studies are discussed in more detail below, ranked according to the kind of intervention.

Pharmacological interventions

Surfactants

Pulmonary surfactant, a surface tension lowering substance, instilled into the middle ear of otologically healthy rats and rats with acute otitis media decreased the mean Po.[15,16] The mean Po of anaesthetised gerbils with OME was found to be significantly higher than the mean Po of healthy gerbils. Rinsing the middle ear with surfactant substantially reduced the mean Po in both the healthy and the diseased animals, whereas rinsing with normal saline had no effect.[17] In another study, the mean Po of gerbils with OME who had been treated with nebulised surfactant, did not differ from the Po of otologically healthy gerbils. As the Po is known to be increased during OME, the authors concluded that nebulised surfactant decreased the Po.[18] Injection of a surface tension lowering substance into the middle ears of rats also reduced the Po.[19] The effect on other ET parameters was not evaluated in any of these studies and none of the studies had a placebo-controlled design.

Beta adrenoceptor agonists

In only one study, performed on 12 healthy dogs, a beta adrenoceptor agonist (intravenous isoproterenol) caused an increase of the perfusion pressure, indicating a deterioration of the passive opening of the ET.[9] On the other hand, intravenous injection of isoprenaline, another beta adrenoceptor agonist, reduced the Po in healthy anaesthetised rats, reflecting an improvement of passive ET function. In rats with acute otitis media, no effect was found. The effect on Pc was not measured in these studies.[16,19] The investigators suggested that isoprenaline acted on the ET by causing secretion of surface tension lowering substances in the ET. During acute otitis media, the ET mucosa of these rats was probably unable to respond to isoprenaline as a result of inflammatory changes. A randomised cross-over study in healthy adults showed that subcutaneously injected terbutaline, another beta adrenoceptor agonist, reduced the Po and Pc, whereas injection of saline solution did not affect passive opening. The effect of terbutaline on active ET function was also studied, but no effect was found.[20] None of the studies was performed in a placebo-controlled fashion.

Decongestants and/or antihistamines

In several studies, the effect of decongestants (alpha adrenoceptor agonists), antihistamines (H1 receptor antagonists) or combination preparations on ET function was studied. Both drugs are assumed to decongest the mucosa of the ET by causing vasoconstriction in the ET. Some studies found a positive effect on ET function,[9,21-25] while others did not.[23,26-29] An improved passive opening of the dog's ET was found after intra-arterial administration of norepinephrine[9] and after topical and intra-arterial administration of pseudoephedrine.[22] These two studies lacked the use of a placebo group. In a cross-over study of 13 children with ventilation tubes owing to OME, the use of an oral decongestant improved active ET function in approximately 50% of the children. The effect on passive ET function was not assessed.[21] In another study of 50 children with ventilation tubes, all of the children who developed an upper respiratory tract infection, received either an oral decongestant (pseudoephedrine) or a placebo. Oral administration of the decongestant had no effect on Po, Pc or active ET function. The children without an upper respiratory tract infection were treated with oral pseudoephedrine-antihistamine or a placebo following a double-blind, cross-over study design. The decongestant-antihistamine treatment showed to be effective in lowering the Pc, but the Po and the active ET function did not change.[23] A total of 36 patients with a dry perforation and ET dysfunction were included in a

Table 1. The effect of different interventions on various parameters of Eustachian tube function.

author	intervention	study population	opening pressure	closing pressure	active ET function	perfusion pressure	sniff test	Valsalva's manoeuvre	sonotubo-metry	clearance time
	surfactants									
Malm et al. (1984)[19]	surface tension lowering substance	healthy rats	+							
White (1989)[15]	surfactant	healthy rats	+							
White et al. (1990)[16]	surfactant	healthy rats and rats with OMA	+							
Fornadley et al. (1994)[17]	surfactant	healthy gerbils and gerbils with OME	+							
Nemechek et al. (1997)[18]	surfactant	gerbils with OME	+							
	beta adrenoceptor agonists									
Sheffield et al. (1970)[9]	isoproterenol	healthy dogs				-				
Malm et al. (1984)[19]	isoprenaline	healthy rats	+							
White et al. (1989)[20]	terbutaline	healthy adults	+	+	=					
White et al. (1990)[16]	isoprenaline	healthy rats	+							
White et al. (1990)[16]	isoprenaline	rats with OMA	=							
	decongestants and / or antihistamines									
Miller (1970)[21]	pseudoephedrine	children with OME			+					
Sheffield et al. (1970)[9]	norepinephrine	healthy dogs				+				
Dempsey et al. (1972)[22]	pseudoephedrine	healthy dogs				+				
Cantekin et al. (1980)[23]	pseudoephedrine	children with OME and URTI	=	=	=					
Cantekin et al. (1980)[23]	pseudoephedrine-chlorpheniramine	children with OME	=	+	=					
Lildholdt et al. (1982)[26]	pseudoephedrine	children with OME	=	=	=					

Virtanen (1982)[27]	pseudoephedrine-chlorpheniramine	adults with induced cold							=	
Doyle et al. (1988)[28]	chlorpheniramine	adults with induced cold			=				=	
Jensen et al. (1990)[24]	xylometazoline	patients with COM and ET dysfunction			=			+		
Doyle et al. (1993)[29]	pseudoephedrine-atropine	adults with induced cold			=					
Olen et al. (1993)[25]	xylometazoline	adults with common cold							+	
	other drugs									
Sugiura et al. (1997)[30]	roxythromycine	healthy guinea pigs								+
Sugiura et al. (1997)[31]	sairei-to	healthy guinea pigs								=
	adenoidectomy									
Bluestone et al. (1975)[32]	adenoidectomy	children with OME	=	=	= / +					
Honjo et al. (1985)[34]	adenoidectomy	children with OME	=		=					
Takahashi et al. (1989)[33]	adenoidectomy	children with OME	=		+					
Dempster et al. (1989)[35]	adenoidectomy	children with OME					=			
Mandel et al. (1992)[36]	adenoidectomy	children with OME	=	=	=					
	ventilation tubes									
Bluestone et al. (1974)[37]	ventilation tubes	children with OME			=					
Neel et al. (1977)[38]	ventilation tubes	children with OME			=					
Beery et al. (1979)[39]	ventilation tubes	children with OME	=	=	=			=		
Knight et al. (1993)[40]	ventilation tubes	children with OME	=							
Bunne et al. (2000)[41]	ventilation tubes	children with OME	-	=	=		=	=		
van Heerbeek et al. (2000)[42]	ventilation tubes	children with OME	-	=	=					

+ indicates improvement; - indicates deterioration; = indicates no effect; when left open the corresponding test was not performed

OMA: acute otitis media, OME: otitis media with effusion, URTI: upper respiratory tract infection, COM: chronic otits media, ET: Eustachian tube

randomised, placebo-controlled study on the effect of a decongestant (xylometazoline chloride 0.1%), applied directly to the pharyngeal opening of the ET. The Valsalva's manoeuvre showed a significant improvement following application of the decongestant, but the pressure equilibration test did not show a difference between the two groups.[24] Nasal application of a decongestant had a positive effect on active ET function measured with sonotubometry in a randomised, double-blind study of 36 adults,[25] but no effect on active or passive ET function was found in another randomised, placebo-controlled study of 40 children with ventilation tubes.[26] In two randomised, placebo-controlled studies of otologically healthy adults with an induced common cold, neither an oral antihistamine nor an oral antihistamine-decongestant preparation had any effect on the ET function measured with a modified pressure equilibration test and sonotubometry or sonotubometry alone.[27,28] Finally, an oral decongestant (pseudoephedrine), combined with atropine, had no effect on active ET function in adults who had an induced rhinovirus cold, in a randomised, placebo-controlled study. Passive ET function was not assessed.[29]

Other drugs

Roxythromycin, a macrolide antibiotic, caused a direct increase in ciliary activity in guinea pigs and a concurrent decrease in the mucociliary clearance time. In addition, roxythromycin increased the superoxide production of neutrophils in the guinea pig's ET. Apparently roxythromycin improves the clearance function of the ET.[30] High dosage of sairei-to, a herbal medicine, also enhanced ciliary activity in guinea pigs, but failed to improve clearance time.[31] The effect of a placebo was not measured in these studies.

Surgical interventions

Adenoidectomy

In 23 children who had been treated for OME with ventilation tubes, active and passive ET functions were measured before and after adenoidectomy. Passive ET function did not change. In most patients, active ET function did not change as well but, in some, the ability to equilibrate positive pressure improved after adenoidectomy. These patients had high Po and Pc prior to adenoidectomy, suggesting obstruction of the ET by the adenoid. The authors suggested that adenoidectomy may only improve ET function if obstruction of the ET is present.[32] In another study, the ET function was measured in 132 children with OME. Ventilation tubes were inserted in all the children and 78 randomly

selected children also underwent adenoidectomy. No difference was found between the mean Po of both groups, but the active ET function was significantly better in the adenoidectomised group.[33] Other investigators did not demonstrate an effect of adenoidectomy on passive or active ET function in children.[34-36]

Ventilation tubes

The effect of ventilation tubes on ventilatory function of the ET was also studied. Most studies did not find significant changes in active or passive ET function over time after insertion of ventilation tubes.[37-40] In two other studies, with large study populations, the insertion of ventilation tubes had no effect over time on active ET function or Pc, but did result in a significant increase in the Po.[41,42] This increase in Po may be caused by a change in the gas composition in the middle ear and the subsequent changes of the middle ear epithelium.

Discussion

Some critical remarks can be made about the reviewed articles. First, most studies unfortunately concerned the effect of interventions on ventilatory function, whereas only a few studies reported the effect on protective or clearance function. These three ET functions are, however, closely related. As all these functions are integrated into one small complex structure, each change of any of these functions may directly affect the other functions. In addition, each intervention may have a positive effect on one of these functions and, at the same time, have a negative effect on another function. For example, a decrease in the Po or the Pc is generally considered to reflect an improvement of the ventilatory function but this decrease may, in some cases, result in a deterioration of the protective function as well. The Po and Pc are assumed to reflect the closing forces of the ET. During active equilibration, these closing forces have to be overcome by contraction of the paratubal muscles but, during nasopharyngeal pressure variations, these forces must be sufficient to keep the ET closed and protect the middle ear. Therefore, we suggest that a decrease of the closing forces can be regarded as an improvement of the ET function as long as the protection of the middle ear is not affected. These considerations are important when the effect on ET function is studied.

Second, the heterogeneity among the reviewed studies was very pronounced. The interventions that were studied varied widely and the different study populations were usually small and not similar (e.g. different animal models, children with OME, healthy adults or adults with induced common cold). In addition, the test methods that were used to assess ET function differed

between the studies. Most investigators studied only one or a few aspects of ET function. Even if the same test methods were used, they were frequently performed differently. This may affect the outcome of the test.[8] As a result of this heterogeneity, it was very difficult to compare the results of the different studies. Therefore, we did not present the quantitative test results but only discussed the effects qualitatively (i.e. whether an effect was found or not).

Third, most studies did not use a control group, although randomised, placebo-controlled trials are the "golden standard" to assess the efficacy of an intervention. Only the studies investigating the effect of a decongestant and/or an antihistamine had a randomised, double-blind, placebo-controlled design, except for the two studies on dogs. Of the studies of the effect of adenoidectomy, only one was a randomised, controlled study.

Although the results were not uniform throughout the different studies and despite the restrictions mentioned above, some conclusions can be drawn from this literature review. The results of this review indicate that the ET function may be improved by medical intervention. Several drugs (surfactants, beta adrenoceptor agonists and decongestants) were shown to have an effect on passive ET function (Po and/or Pc). Unfortunately, in most of these studies, active ET function was not investigated. Nearly all studies that did investigate active ET function as well did not find an effect. Active and passive opening of the ET may be improved by increasing the concentrations of surfactant or by decongesting the mucosa of the ET, but it seems premature to recommend any of the interventions reviewed in this paper to improve ET function in humans.

Roxythromycin enhanced the clearance capacity of the guinea pigs' normal ET. These effects seem promising, but whether drugs are also effective to improve mucociliary clearance in humans or when the mucociliary clearance is impaired (e.g. during OME) has not yet been studied.

The adenoid is assumed to play a role in the pathogenesis of OME. One of the suggested mechanisms is that the adenoid obstructs the ET, causing impairment of the ET ventilatory function. As adenoidectomy caused improvement of the active ET function in only a few studies and the closing forces (Po and Pc) did not change at all, this hypothesis seems less likely. Improvement of the ET function may be limited to a small proportion of children with obstructing adenoids. The adenoid may also be involved in the aetiology of OME in another way.

Ventilation tubes restore hearing in children with OME but may have an adverse effect on ET function. The aeration of the middle ear may cause changes in the middle ear epithelium and the secretion of mucus, which result in an increase of

the closing forces.[42] Whether this impairment of the ET function persists after the extrusion of the tubes, and may even affect the middle ear, is unknown.

Conclusions

ET function can be improved therapeutically. However, based on the results of this review, it seems premature to recommend any of the interventions reviewed in this paper to improve ET function in humans. When the effect of a certain intervention is studied, one should consider that each intervention that has a positive effect on a particular aspect of the ET function may have negative effects on the middle ear system as well. Surfactants, for example, may lower the closing forces to such an extent that the protective function is no longer guaranteed. More studies, preferably randomised, placebo-controlled trials, should be conducted to assess the efficacy of different interventions on ET function and to reveal the cases in which they are effective. Those studies will extend our knowledge of the ET function and the role of ET dysfunction in the pathogenesis of OME and other middle ear diseases. Besides, if ET function can be improved, the clinical relevance of this improvement regarding OME and other middle ear diseases still has to be revealed. Improvement of the ET function will not necessarily result in prevention or resolution of OME. Although ET dysfunction is assumed to play a role in the pathogenesis of OME and other middle ear diseases, many other factors affect the development of these diseases as well.

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Chapter 5

Eustachian tube function after the insertion of ventilation tubes in children

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Abstract

This study was performed to assess the effect of the insertion of ventilation tubes and the subsequent aeration of the middle ear on Eustachian tube (ET) function in children. Manometric ET function tests were performed repeatedly during 3 months, after the placement of ventilation tubes in 83 children with otitis media with effusion (OME). Opening and closing pressures (passive ET function) and tubal function group (active ET function) were measured. Analysis of the results showed a significant increase in opening pressure over time, while the closing pressure did not change. Tubal function group did not change and remained at the same poor level. Therefore, the relatively high opening and closing pressures and especially the poor active ET function in these children were more likely to be a causal factor of OME than a result. Certain children may have poor intrinsic ET function, which makes them more susceptible to OME.

Introduction

Otitis media with effusion (OME) is a common disease during childhood. Nearly every child will suffer from at least one episode of OME before the age of four years.[1] As a result of the high incidence, OME has become the most frequent reason for surgery in young children.[2] Different surgical procedures, including myringotomy, insertion of ventilation tubes, adenoidectomy or combinations are used for OME treatment.[3,4]

The pathogenesis of OME is multifactorial, but a negative middle ear pressure,[5-8] immunological abnormalities[9,10] or a combination of these factors is assumed to play a central role in the pathogenesis of OME.

The exact mechanism responsible for persistent negative middle ear pressure still remains unclear. Middle ear pressure is influenced by the diffusion of gases between the middle ear cavity and the surrounding tissues and by ventilation of the middle ear through the Eustachian tube (ET). Impaired gas diffusion is speculated to be an important factor in the development of persistent negative middle ear pressure.[7,11] Normally, equilibration of negative middle ear pressure is achieved by periodical active opening of the ET. Impaired ventilation of the middle ear caused by functional obstruction of the ET[5,6] or closing failure combined with habitual sniffing[8] is assumed to cause persistent negative middle ear pressure. However, it is not clear whether this ET dysfunction is a cause or a result of the effusion in OME. ET function may either deteriorate as a result of the presence of effusion in the middle ear cavity or ET function may be intrinsically poor in some children who, as a result, develop persistent OME, while other children with good ET function do not develop OME or only short-term OME.

Many other factors that have been described as prognostic or pathogenic for OME[12-15] probably influence the occurrence of OME through their effect on ET function, the diffusion of gases or the immunological response.

The insertion of ventilation tubes is assumed to be a symptomatic treatment. Ventilation tubes take over the function of the ET by resolving the effusion and ventilating the middle ear. However, besides being a substitute for ET function, the insertion of ventilation tubes may affect ET function as well. The aim of this study was to assess the effect of the insertion of ventilation tubes and the subsequent aeration of the middle ear on ET function in children with OME.

Materials and methods

The study population comprised 83 children, 38 boys and 45 girls, with a mean age of 6.3 years (range 1.7-12.1 years). All the children were treated with

ventilation tubes at the Department of Otorhinolaryngology of the University Medical Centre or the Canisius Wilhelmina Hospital in Nijmegen, because of persistent OME. In total, 138 ears were examined (71 left ears and 67 right ears). On average, manometric ET function tests (forced response test and pressure equilibration test) were performed 2 hours, 1.5 weeks and 13 weeks postoperatively. Children with syndromes that may affect middle ear function (e.g. Down's syndrome and cleft palate) were excluded. Parental consent was obtained in all cases.

Equipment

A recently calibrated TYMP87 middle ear analyser (Rexton Danplex A/S, Copenhagen, Denmark) was used for the measurements. Pressure applied by the pump ranged from 600 daPa to -600 daPa, with a pump rate of 50 daPa/s.

Procedure

Before surgery, all the parents filled in a questionnaire about their child's otorhinolaryngological history. Under general anaesthesia, all the children underwent unilateral or bilateral myringotomy with aspiration of the effusion when present. Subsequently, ventilation tubes were inserted.

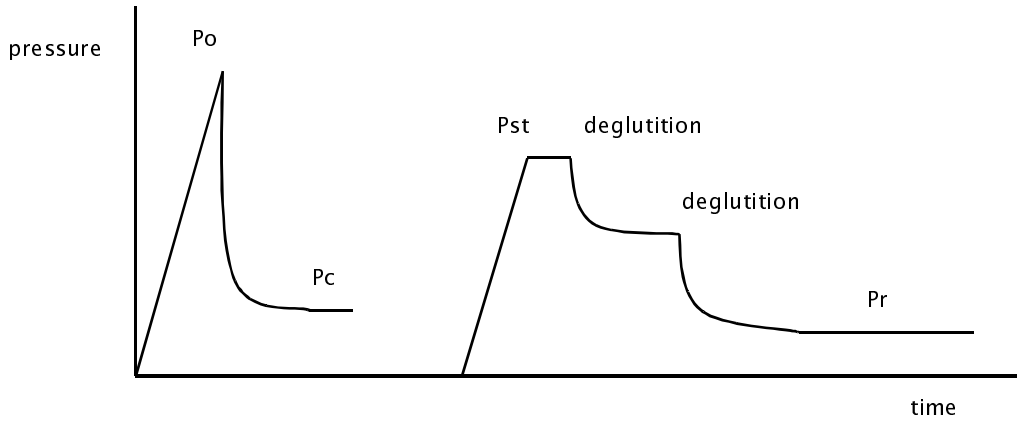

Figure 1. Examples of a recording of the forced response test [left] with opening (Po) and closing pressure (Pc), and the pressure equilibration test [right] with starting (Pst) and residual pressure (Pr).

The ET function was assessed two hours after operation. An example of an ET function measurement is shown in Figure 1. Passive ET function was assessed by measuring the opening pressure (Po) and the closing pressure (Pc) (forced response test). The Po was the pressure at which the ET opened spontaneously, while the Pc was the residual pressure after passive opening. In a previous study, the results of the forced response test showed a downward shift with repeated

measurement. Therefore Po and Pc were recorded three times during each postoperative measurement, hereafter referred to as session. The means of the three Po and Pc were used for analysis.[16]

Active ET function was assessed by measuring the children's ability to equilibrate positive and negative pressures (pressure equilibration test). A positive or negative pressure was applied to the middle ear and the effect of repetitive deglutitions (the children were asked to swallow some lemonade) on this pressure was recorded. The pressure equilibration test was performed only once during each session, since the categorised results of the test showed good reproducibility.[16] The residual pressure (Pr) after several deglutitions was recorded. Based on the Pr, each subject was classified into one of four tubal function groups according to Elner et al.[17] The subjects in group I were able to equilibrate positive and negative pressures completely (Pr<10 daPa and >-10 daPa, respectively). Group II subjects could equilibrate positive and negative pressures partially (Pr>10 daPa or <-10 daPa, respectively). Group III subjects could equilibrate positive pressure completely or partially, but were not able to equilibrate negative pressure. The subjects in group IV could not equilibrate positive or negative pressures. The measurements were performed with starting pressures of 200 and -200 daPa, respectively. In some subjects a starting pressure of 200 daPa could not be applied, because the ET opened spontaneously before 200 daPa was reached. In these subjects the test was performed with starting pressures of 100 and -100 daPa in all three sessions. The ET function tests are described in more detail elsewhere.[16]

Statistical analysis

All data were analysed using the SAS statistical package (SAS Institute, Cary, NC, USA). Univariate analyses were performed on the data from the ears that were measured first. Only one ear of each child was used for univariate analyses, because the results of left and right ears were highly correlated. Differences in mean Po and Pc over time were tested using the paired t-test and differences in tubal function group over time were tested using the McNemar test.

The chi-square test and the Student's t-test were used to study the differences in active and passive ET function between different subgroups. For each comparison the children were divided into two subgroups based on one of the following criteria: previous adenoidectomy, previous treatment with ventilation tubes, four or more annual episodes of upper respiratory tract infection and the presence of effusion in the middle ear at the time of surgery.

In order to adjust for comparison of multiple test sessions, Po and Pc from all ears were also analysed after logarithmic transformation using a linear mixed model (SAS procedure MIXED). The effect of order of measurement, i.e. whether the left ear or the right ear was measured first, was also studied in this model. We used time (3 levels) and order of measurement (2 levels) as additive fixed effects. An unstructured covariance matrix was used. Some children's ET did not open even when the maximum pressure (i.e. 600 daPa) was applied. To be able to include these ears in the linear mixed model, the Po of these ears was estimated to be 650 daPa, based on the variance of all Po. The corresponding Pc remained missing, because no reliable estimation of Pc could be made.
The ears in tubal function groups I and II were omitted from all the analyses, because these groups contained no or only a few ears. Data from the children with missing values at one of the sessions due to obstruction or early extrusion of the ventilation tube, otorrhea or poor co-operation of the child, were included in the analyses, because the occurrence of these missing values was assumed to be random and because the results of these children corresponded with the results of the children without missing values.

Results

Forced response test
Figure 2 shows the mean Po and Pc ± 2 x standard error of the mean (SEM) of all the ears at 2 hours, 1.5 weeks, and 13 weeks based on the results of the linear mixed model. Both univariate analysis and the linear mixed model showed a significant increase in Po over time (p=0.003, linear mixed model). The increase in Po between the first and the second sessions was more pronounced (30 daPa in 1.5 weeks, p=0.01) than the increase between the second and third sessions (18 daPa in 11.5 weeks, p=0.06). Order of measurement, i.e. whether the left or the right ear was measured first, did not affect (p=0.86) the Po. No effect of time and order of measurement on Pc was found (p=0.34 and p=0.24, respectively).

Pressure equilibration test
Figure 3 shows the distribution over the tubal function groups at 2 hours, 1.5 weeks and 13 weeks. Only a few children were able to equilibrate negative pressure (4%, 2% and 3% at the three sessions, respectively) and none of these children were able to equilibrate negative pressure at all three sessions. Most of the children had poor ET function, i.e. tubal function group III or IV. No

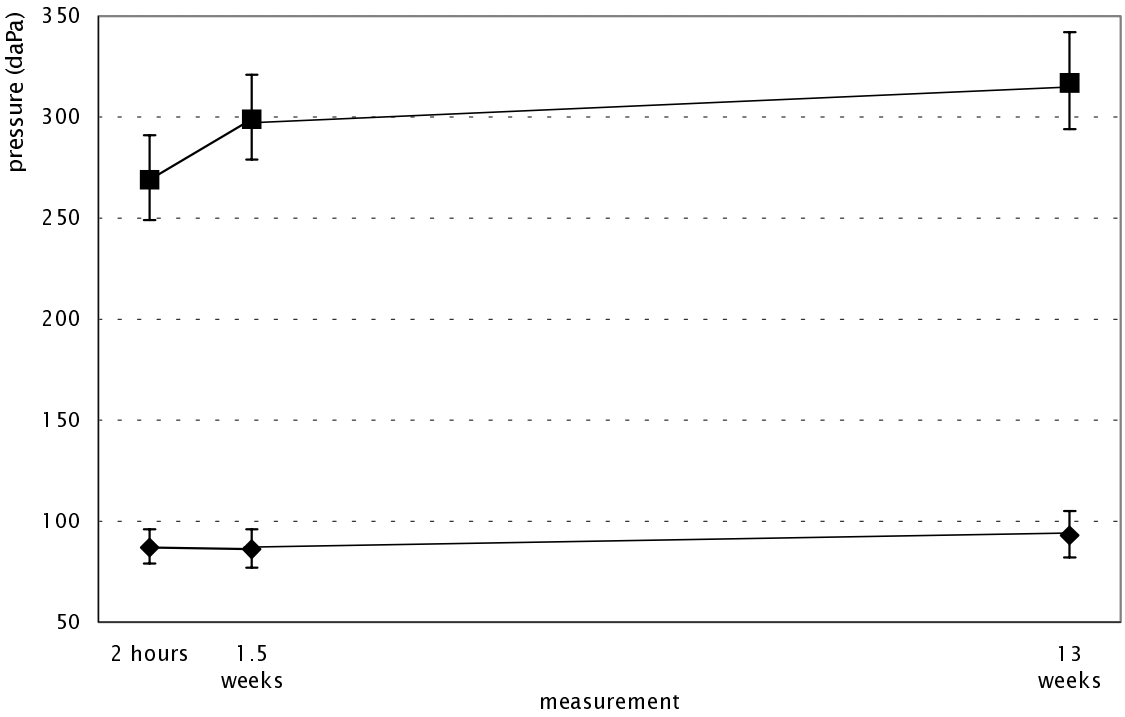

Figure 2. Mean opening (solid square) and closing pressure (solid diamond) [± 2 SEM] at 2 hours, 1.5 weeks and 13 weeks, based on the results of the linear mixed model.

significant change in tubal function group was found during the 3 months follow-up period using McNemar test ($p \geq 0.2$), but there was considerable intraindividual variability over time. ET function group was found to fluctuate over time within individuals.

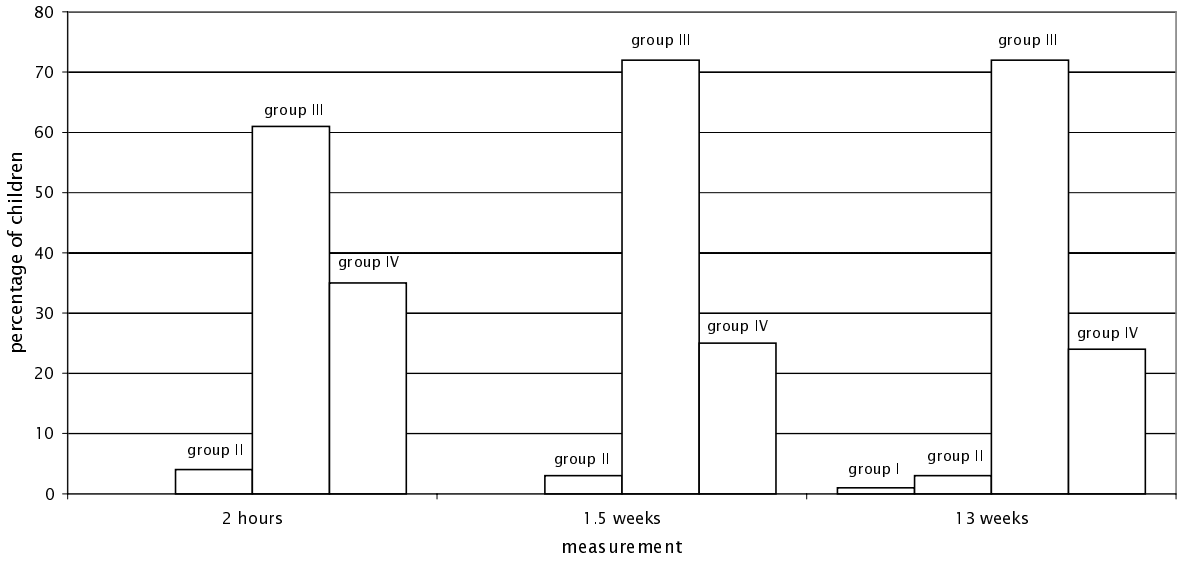

Figure 3. Active Eustachian tube function at 2 hours, 1.5 weeks and 13 weeks.

Associations

Po and Pc were found to be significantly higher in tubal function group IV than in group III at all three sessions (all p≤0.005). Two hours postoperatively, Po was 79 daPa (95% confidence interval [CI]: 26-132 daPa) higher in group IV, while Pc was 46 daPa (95% CI: 19-73 daPa) higher. At 1.5 and 13 weeks, these differences were even more pronounced.

Table 1. Active and passive Eustachian tube function of each subgroup at the first session.

subgroups	n	Po (daPa)	SD (daPa)	Pc (daPa)	SD (daPa)	group III (%)	group IV (%)
previous adenoidectomy							
yes	43	282	120	114	63	63	37
no	39	273	116	102	60	63	37
previous VT							
yes	42	287	126	109	68	59	41
no	40	268	109	108	54	68	32
URTI							
≥4	44	270	102	109	54	68	32
<4	38	286	135	108	70	57	43
effusion							
present	47	302*	136	125*	68	54*	46*
not present	27	234*	74	78*	44	77*	23*

VT: ventilation tubes; URTI: upper respiratory tract infection

* difference statistically significant

Table 1 shows the results of the active and passive ET function of the different subgroups at 2 hours postoperatively. Univariate analysis did not show any significant differences in active and passive ET function between children with or without previous adenoidectomy, ventilation tubes or upper respiratory tract infections at any of the three sessions. However, the presence of effusion at the time of surgery was found to affect active and passive ET function. In 27 out of the 83 children, the effusion in the ear that was used for univariate analysis had resolved prior to the insertion of ventilation tubes. In these ears, no effusion was seen during surgery. In 47 ears, effusion was present and in 9 ears this information was missing. The ears with and without effusion were compared. At 2 hours postoperatively, the mean Po was found to be 68 daPa (95% CI: 11-124 daPa) higher in the ears with effusion, while the Pc was 47 daPa (95% CI: 17-76 daPa) higher. Active ET function was found to be poorer in the ears with

effusion: 46% of the ears with effusion had tubal function group IV compared to 23% of the ears without effusion (p=0.003). At 1.5 and 13 weeks, these differences in Po, Pc and tubal function group between the ears with and without effusion at the time of surgery still existed, but they were smaller and no longer statistically significant.

Discussion

The insertion of ventilation tubes had no effect over time on tubal function group or Pc, but did result in a significant increase in Po. If it is hypothesised that Po and Pc increase and active ET function deteriorates as a result of effusion in the middle ear (i.e. ET dysfunction is a result of the effusion), then we would have found a decrease in the Po and Pc and an improvement in active ET function when the effusion is resolved by inserting ventilation tubes. However, Po and Pc did not decrease (Po even increased) and active ET function remained at the same poor level. Therefore, the relatively high Po and Pc and especially the poor active ET function in these children were more likely to be a cause than a result of the effusion, although it cannot be ruled out that effusion in the middle ear may also affect ET function. Apparently, some children have poor intrinsic ET function, which makes them more susceptible to OME and maybe to other middle ear diseases as well.

Po is assumed to reflect the total closing forces, i.e. the luminal and extraluminal forces, of the ET. Pc is assumed to represent the extraluminal forces (pressure of the cartilage and other surrounding tissues, etc.) The difference between Po and Pc is assumed to represent the luminal forces (mucosal factors, surface tension, viscosity of secretions, etc.).[18-20] As Po increased and Pc remained constant, it may be inferred that the insertion of ventilation tubes caused an increase in the luminal forces. It has been shown that the insertion of ventilation tubes caused a change in the middle ear gas composition.[21] Several authors found that this change in middle ear gas composition in vivo or in vitro caused changes in the middle ear epithelium.[22-25] Changes in the middle ear epithelium and/or possibly subsequent changes in the secretion of mucus and muco-adhesive substances may result in higher luminal forces and thus higher Po. This suggests that the insertion of ventilation tubes may even have an adverse effect on ET function, because higher Po and Pc were associated with poorer active ET function.

Po and Pc were significantly higher and active ET function was significantly poorer in the ears with effusion on the day of surgery. In both subgroups, tubal function group and Pc did not change, while Po increased throughout the follow-

up period. Based on the discussion above, the ears in which no effusion was found at the time of tube insertion may have had better intrinsic ET function than the ears in which effusion was present at the time of surgery. It may even be hypothesised that ET function also affects the degree of persistence of the effusion, besides influencing the occurrence of effusion.

The literature on the effect of the insertion of ventilation tubes and the subsequent aeration of the middle ear on ET function is limited. Most studies did not find significant changes in active or passive ET function over time.[26-29] However, most of these studies comprised small study populations, used different time intervals and studied only active or passive ET function. Recently, Bunne et al.[30] have reported that Po increased significantly over time, while active ET function did not change. Although they also reported a significant increase in the mean Pc, the median Pc remained fairly stable. Apparently their results were positively skewed. Thus our results correspond with theirs.

Conclusions

Poor ET function is more likely to be a causal factor of OME than a result, because Po and Pc did not decrease (Po even increased) and active ET function remained at the same poor level after the insertion of ventilation tubes and subsequent drainage of the effusion. Certain children may have poor intrinsic ET function, which makes them more susceptible to OME and maybe to other middle ear diseases as well. The increase in luminal forces after the insertion of ventilation tubes, believed to be caused by mucosal changes due to altered middle ear gas composition, may even have an adverse effect on passive ET function. These findings indicate that ET function tests may be a useful diagnostic tool for discriminating between different degrees of middle ear disease. In addition, treatment strategies that potentially affect ET function, such as adenoidectomy, may be more effective in children with poor ET function. These prospects for the application of ET function tests in the diagnosis and management of OME should be investigated in further studies.

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Chapter 6

No effect of a nasal decongestant on Eustachian tube function in children with ventilation tubes

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Abstract

Objectives/Hypothesis: The aim of this study was to assess the effect of a topical decongestant on Eustachian tube (ET) function in children with ventilation tubes due to persistent otitis media with effusion (OME).

Design: A randomised, double-blind, placebo-controlled study.

Setting: The outpatient departments of a secondary referral hospital and a tertiary referral hospital.

Patients and Methods: ET function was measured before and after intranasal administration of five drops of 0.05% xylometazoline hydrochloride or placebo in eighty randomly selected children with ventilation tubes due to OME.

Results: Xylometazoline nose drops had no effect on the ventilatory or the protective function of the ET.

Conclusions: Topical decongestants do not have a positive effect on the ET function in children. The use of topical decongestants to prevent or treat OME in children is therefore not justified and should be discouraged.

Introduction

The Eustachian tube (ET) is crucial for normal middle ear function. Three functions of the ET are recognised: ventilation, protection and clearance of the middle ear. Frequent active opening of the ET allows ventilation of the middle ear cavity and prevents the development of a persistent negative middle ear pressure, caused by gas exchange between the middle ear cavity and the surrounding mucosa.[1] The ET, which is collapsed at rest, also protects the middle ear against ascending secretions and micro-organisms from the nasopharynx and against nasopharyngeal pressure variations. In addition, the ET with its mucociliary epithelium is involved in local defence against pathogens and is concerned with clearance of secretions and debris from the middle ear towards the nasopharynx.

Children suffering from persistent otitis media with effusion (OME) were found to have poor ET function.[2-4] This ET dysfunction did not improve after the insertion of ventilation tubes and the subsequent resolution of the effusion.[2] These findings show that the poor ET function in these children is more likely to be a cause of the effusion than a result. Apparently, some children have poor intrinsic ET function, which makes them more susceptible to OME and other middle ear diseases. If the ET function can be improved therapeutically in these children, their susceptibility to OME may be reduced. Such treatment strategies may be effective to prevent the development of persistent OME. Topical decongestants are thought to be one of these treatment strategies.

The effect of topical decongestants on ET function has been studied before.[5-7] However, only one of these studies was performed on children.[7] No effect of a nasal decongestant spray was found, but the size of the study population was so small that only very large differences between the decongestant and the placebo could be detected. The aim of this study was to assess the effect of a topical decongestant on the ventilatory and protective function of the ET in eighty children with ventilation tubes due to persistent OME.

Patients and Methods

Eighty children, who had been treated with ventilation tubes due to persistent OME and who still had the tubes in situ, were invited to participate in the study. Children with syndromes that may affect middle ear function (e.g. Down's syndrome, cleft palate), children with a history of chronic nasal inflammation and children who used any kind of nasal medication were excluded. Parental consent was obtained in all cases.

Different ET function tests (forced response test, pressure equilibration test and sniff test) were performed before and after the administration of a nasal decongestant or placebo according to a randomised, double-blind, placebo-controlled study design. The active drug was 0.05% xylometazoline hydrochloride nose drops and normal saline was used as a placebo. Immediately after the first measurement of the ET function, five drops were instilled into each nostril. To obtain maximum exposure of the ET to the nose drops, the drops were applied in supine position with the head turned 15 degrees toward the ipsilateral ear. The child was kept in supine position for 1 minute. The second measurement was performed 10-15 minutes after the administration of the nose drops.

Eustachian tube function tests

First, the presence and permeability of the ventilation tubes were confirmed otoscopically. If both ventilation tubes were functioning, the right ear was measured first. Successively, the forced response test, the pressure equilibration test and the sniff test were performed using a TYMP87 middle ear analyser (Rexton Danplex A/S, Copenhagen, Denmark). The tests provide information about the passive and active ventilatory function (forced response test and pressure equilibration test, respectively) and the protective function (sniff test) of the ET.

The forced response test measures the opening pressure (Po) and the closing pressure (Pc). The Po is the pressure at which the ET opens spontaneously when the pressure in the middle ear is gradually increased. After opening of the ET, the pressure pump is turned off and the ET closed spontaneously. The Pc is the residual pressure after passive closure. The Po is assumed to reflect the total closing forces, i.e. the luminal and extraluminal forces, of the ET and the Pc is assumed to represent the extraluminal forces (pressure of the cartilage and other surrounding tissues). The difference between Po and Pc is assumed to represent the luminal forces (mucosal factors, surface tension, viscosity of secretions, etc.). Po and Pc were recorded three times and the means of the three Po and Pc were used for further analysis as described elsewhere.[8]

Active ventilatory function of the ET was assessed by measuring the children's ability to equilibrate positive and negative pressures (pressure equilibration test). A positive or negative pressure (+100 and -100 daPa respectively) was applied to the middle ear and the residual pressure (Pr) after several deglutitions (the children were asked to swallow some water) was recorded. Based on the Pr, each subject was classified into one of four tubal function groups according to

Elner et al.[9] The subjects in group I were able to equilibrate positive and negative pressures completely (Pr<10 daPa and >-10 daPa, respectively). Group II subjects could equilibrate positive and negative pressures partially (Pr>10 daPa and <-10 daPa, respectively). Group III subjects could equilibrate positive pressure completely or partially, but were not able to equilibrate negative pressure. The subjects in group IV could not equilibrate positive or negative pressures. The forced response test and the pressure equilibration test are described in more detail elsewhere.[8]

To evaluate the protection of the ET against extreme negative nasopharyngeal pressure, the subject was asked to sniff forcefully five times (sniff test). If the middle ear pressure decreased at least once, the test was considered as positive. A positive sniff test is assumed to indicate poor protective function of the ET.[10,11]

Statistical analysis

In forty percent of the children, both ears were measured. As the right ear was always measured first in these children and the results of the left and right ET are highly correlated, the left ears of these children were analysed separately.

The Po and Pc were considered to be normally distributed and described with means and standard errors of the mean (SEM). Means were analysed with the Student's t-test when both treatment groups were compared and with the paired t-test when values before and after application of the nose drops were compared. The results of the pressure equilibration test were analysed for number of ears in each tubal function group and the results of the sniff test were analysed for number of sniff-positive and sniff-negative ears. Differences between the two groups were analysed with the chi-square test and within one group with the McNemar test. All data were analysed using the statistical package SPSS.

Power analysis predicted that it would be necessary to have 40 ears in each group to show a decrease of 50 daPa in Po and 30 daPa in Pc and an improvement of 25% in the results of the pressure equilibration test and the sniff test with a power of 90% at the 0.05 significance level. These changes were considered clinically significant.

Results

A total of 80 children were included in the study, 40 in each group. The mean age of the children at randomisation was 6.4 years (SEM=0.2) in the xylometazoline group and 6.0 years (SEM=0.3) in the placebo group. The xylometazoline group consisted of 15 boys and 25 girls and the placebo group

consisted of 23 boys and 17 girls. No side effects of the medication were encountered. At baseline, no substantial differences in mean Po and Pc, number of ears in each tubal function group and results of the sniff test were found between the xylometazoline and the placebo group.

Forced response test

In Figure 1 the mean Po and Pc (± 2 SEM) before and after the administration of the xylometazoline or placebo nose drops are presented. No significant changes in mean Po and Pc were found as a result of the administration of either xylometazoline or placebo nose drops. In the xylometazoline group, the Po decreased with 2 daPa (SEM=6 daPa) and the Pc increased with 1 daPa (SEM=5 daPa).

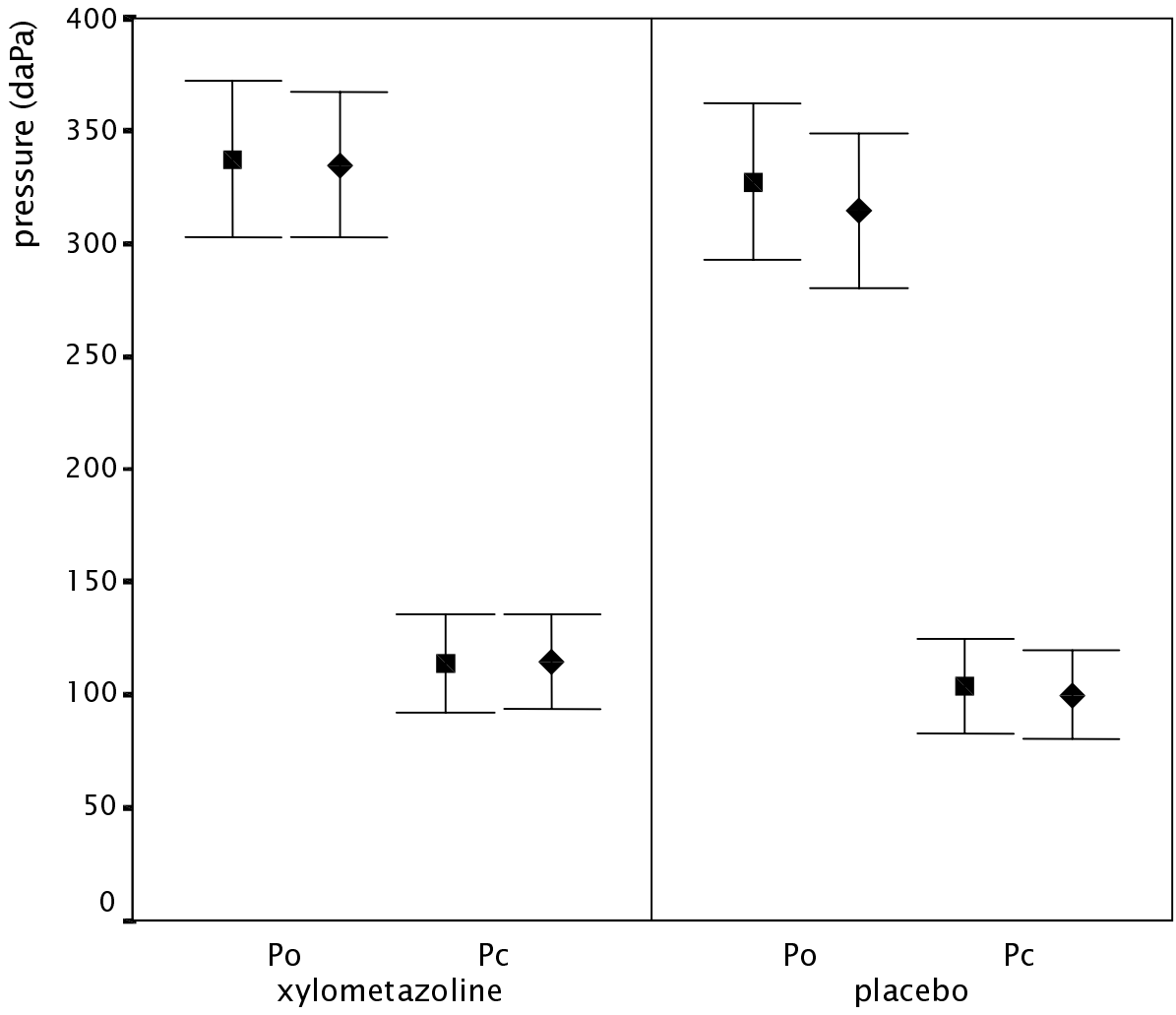

Figure 1. Mean opening (Po) and closing (Pc) pressures (± 2 SEM) before (solid square) and after (solid diamond) the administration of xylometazoline and placebo nose drops. (n=80)

Pressure equilibration test

Table 1 shows the results of the pressure equilibration test. Practically all the children had poor active ET function, i.e. tubal function group III or IV. Only one child (in the xylometazoline group) was able to equilibrate negative pressure, i.e. tubal function group II, before and after the application of the nose drops. No significant changes in active ET function were observed following the application of the nose drops in the xylometazoline or the placebo group (p=0.5 for both groups).

Table 1. Number of ears in each tubal function group before and after the administration of xylometazoline or placebo nose drops. (n=79)

	before nose drops		after nose drops	
	group III	group IV	group III	group IV
xylometazoline	12 *(31%)*	27 *(69%)*	15 *(38%)*	24 *(62%)*
placebo	11 *(28%)*	29 *(72%)*	14 *(35%)*	26 *(65%)*

Sniff test

Seven children (3 in the xylometazoline group, 4 in the placebo group) were not able to perform the sniff test. Table 2 shows the results of the remaining 73 children. Approximately 15-20% of the children in both groups was able to create a negative middle ear pressure by sniffing forcefully (i.e. a positive sniff test). The results of the sniff test did not change after the application of the xylometazoline nose drops (p=0.5) nor did they change after the application of the placebo nose drops (p=0.7).

Table 2. Results of the sniff test before and after the administration of xylometazoline or placebo nose drops. (n=73)

	before nose drops		after nose drops	
	negative	positive	negative	positive
xylometazoline	31 *(84%)*	6 *(16%)*	29 *(78%)*	8 *(22%)*
placebo	29 *(81%)*	7 *(19%)*	27 *(75%)*	9 *(25%)*

In the group of left ears that were analysed separately no changes in the results of the forced response test, the pressure equilibration test and the sniff test were found after the administration of xylometazoline or placebo nose drops. In addition, no differences were found between the left and right ear in these children.

Discussion

Xylometazoline is a sympaticomimetic agent that causes vasoconstriction when applied locally, resulting in decongestion of the mucosa. The effect occurs within a few minutes and lasts for 5-6 hours. Xylometazoline and other topical decongestants have been and still are widely used to prevent or treat OME and acute otitis media. The rationale behind this treatment is that these decongestants are supposed to have a positive effect on the ET function. They are assumed to improve the passive and active opening of the ET, thus preventing the development of a persistent negative middle ear pressure and the accumulation of effusion.

In this study, five drops were instilled into each nostril with the child in supine position. Subsequently the child was kept in supine position for 1 minute. In this way maximum exposure of the nasopharyngeal orifice of the ET to the nose drops was obtained.[12,13] Although the degree of exposure remains uncertain, the exposure is at least equal to the exposure that is achieved when decongestant nose drops or spray are applied by the patients themselves or their parents. More likely, the exposure of the ET to the decongestant in practice is less than it is in this study.

Using different tests, no effect of xylometazoline on ET function was found, neither on the active and passive ventilatory function nor on the protective function. Since poor ET function is known to be one of the causative factors of OME, most children were found to have poor ventilatory function and approximately 15-20% of the children had poor protective function (i.e. a positive sniff test) in this study. These findings are in agreement with other studies on children with ventilation tubes.[2,4,14]

Only a few others studied the effect of topical decongestants on ET function. In one study, a randomised, placebo-controlled study, the effect of a decongestant (0.1% xylometazoline chloride) sprayed directly towards the pharyngeal opening of the ET was measured in 36 patients, mainly adults, with a dry perforation and ET dysfunction. The Valsalva's manoeuvre showed a significant improvement following application of the decongestant, but the pressure equilibration test did not show a difference between the two groups.[5] In another randomised, double-blind study of 34 adults with normal ET function, nasal application of a decongestant had a positive effect on active ET function measured with sonotubometry.[6] No effect on active or passive ET function was found in a third randomised, placebo-controlled but small (n=40) study of children with ventilation tubes.[7] The different results of these studies suggest that topical decongestants may only be effective if the ET function is already quite normal,

e.g. in otologically healthy adults. However, more evidence is needed to support that hypothesis.

Conclusions

The results of this study demonstrate that topical decongestants are not effective in improving ET function in children with poor ET function, i.e. most children with OME. The widespread use of topical decongestants to prevent or treat OME in children is therefore not justified and should be discouraged.

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Chapter 7

Effect of exogenous surfactant on ventilatory and clearance function of the rat's Eustachian tube

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Abstract

Hypothesis and Background: The Eustachian tube (ET) has three important functions with respect to the middle ear: ventilation, clearance and protection. Surfactants are assumed to be important to maintain these functions. Administration of exogenous surfactant may therefore be effective to improve the ET function. This randomised, double-blind, placebo-controlled study was designed to investigate the effect of exogenous surfactant on the ET function in rats.

Material and Methods: Exogenous surfactant was administered into the middle ear of 10 otologically healthy rats, while 10 other rats received placebo. The effect on the opening and closing pressure (passive ventilatory function) and the dye clearance time (clearance function) of the rat's ET was measured.

Results: A significant decrease in the opening pressure was found after the administration of surfactant. Both surfactant and placebo caused an increase in the closing pressure. A serious disturbance of the dye clearance time was induced in 13 rats and the test failed in one rat. In the remaining 6 rats no significant difference in the dye clearance time could be found between the two groups.

Conclusions: Exogenous surfactant decreases the closing forces of the ET even in otologically healthy rats. No significant effect on the mucociliary clearance was found, but this may be due to the small number of rats. Additional randomised, double-blind, placebo-controlled trials, should be conducted to determine the clinical relevance of these changes and to further assess the effect of surfactant on the ET function.

Introduction

The rat is a very suitable model for detailed anatomical and pathophysiological studies of the middle ear and the Eustachian tube (ET).[1-3] The morphology, anatomy and physiology of the rat's middle ear and ET do not differ fundamentally from that of humans. As in man, the rat's ET is important for ventilation, protection and clearance of the middle ear. These functions are closely related and turn the ET into a complex structure that plays an important role in the physiology and pathophysiology of the middle ear.

Regulation of the middle ear pressure depends on several factors. The ventilatory function of the ET and the diffusion of gasses into and out of the middle ear are assumed to be the most important, but middle ear pressure is also affected by the production and elimination of secretions in the middle ear. Intermittent ventilation of the middle ear is established by contraction of the tubal muscles, causing active opening of the ET and allowing ventilation of the middle ear cavity.[4] Frequent opening of the ET is necessary, since gasses are constantly absorbed from the middle ear cavity.[5] Without opening of the ET, a negative middle ear pressure will develop.[6]

Clearance of secretions from the middle ear into the nasopharynx is established by the mucociliary epithelium and the pumping activity of the ET. The mucociliary epithelium lines the ventral part of the ET and is continuous with tracts of ciliated epithelium in the middle ear.[7] It is composed of secretory cells, ciliated cells and basal cells. Mucus, released from the secretory cells, forms a "micron"-thick mucus blanket that covers the epithelium. Carrying dead cells, cell-debris and foreign particles such as dust and bacteria this mucus blanket is transported by the synchronised ciliary movements towards the nasopharyngeal end of the ET.[2,7] Both cilia and mucus are essential for normal mucociliary transport. Any disturbance of either the cilia or the mucus may immediately affect normal mucociliary clearance.[8,9] In addition, secretions are also expelled from the middle ear by the pumping action of the ET.[10,11] During active opening of the ET by contraction of the tubal muscles, excess secretions are sucked into the posterolateral part of the ET. Relaxation of the tubal muscles and subsequent closure of the ET result in propulsion of assembled fluid towards the nasopharyngeal end of the ET. Repeated opening and closure of the ET finally clear the secretions into the nasopharynx. This muscular clearance is of particular importance when the secretion's volume is large.[12]

Surfactants, produced by the ET epithelium, are assumed to be important to maintain normal ET function. A relative deficiency or an altered production of ET surfactant may cause a disturbance of the ET functions.[13] Exogenous surfactant

was found to reduce the pressure required to open the ET in two previous studies.[14,15] However, both studies were not designed double-blind, placebo-controlled nor did they study the effect on the closing pressure of the ET. Moreover, it is conceivable that administration of exogenous surfactant improves the clearance function of the ET as well, because a significant increase in mucociliary transport was found after the application of surfactant, both in vitro and in vivo.[16,17] The aim of this study was to investigate the effect of exogenous surfactant on the opening and closing pressure (Po and Pc, respectively) as well as the mucociliary clearance function of the rat's ET in a double-blind, placebo-controlled fashion.

Material and Methods

Twenty Wistar rats, weighing 300 to 550 grams, were used in this study. All rats were anaesthetised by intraperitoneal administration of 0.1 ml Dormicum® / 100 g (Janssen Pharmaceutica, Beerse, Belgium) and an intramuscular injection of 0.05 ml Hypnorm™ / 100 g (Roche, Mijdrecht, the Netherlands). They were placed in the left lateral recumbent position. Two incisions were made in the right tympanic membrane. One incision was used to inject the surfactant or placebo and the dye that was used for the clearance test. The other incision served as a vent. Preceding the injection, the baseline Po and Pc were measured and the difference between the Po and Pc was calculated. Subsequently, 40 microliters surfactant or placebo were injected into the middle ear. The surfactant was derived from bovine lungs (surfactant-TA), supplemented with three synthetic phospholipids, and contained phospholipids at a total concentration of 25 mg/ml. This concentration is clinically used to lower alveolar surface tension in neonates. Normal saline was used as placebo. At random, ten rats received surfactant and ten rats received placebo. The Po and Pc were measured again 1 as well as 10 minutes after administration. After the final Po/Pc measurement, the rats were killed by exsanguination and the dye clearance time (DCT) was measured.

Forced response test: Po and Pc measurement

The external ear canal was sealed airtight with the probe of a TYMP87 middle ear analyser (Rexton Danplex A/S, Copenhagen, Denmark). Before taking the measurements, a test was performed to verify that there was no leakage. Subsequently, the Po and Pc were measured six consecutive times. The Po was assessed by increasing the pressure in the middle ear until the ET opened spontaneously. This passive opening of the ET was indicated by a sudden

decrease in the pressure. The maximum pressure was recorded as the Po. Immediately after opening of the ET, the pump was turned off and the ET closed spontaneously. The Pc was the residual pressure after passive closure of the ET.

Clearance test: DCT measurement

Immediately after the last measurement of the Po and Pc, the rats were sacrificed. Their lower jaw was removed carefully and the soft palate was incised on the left lateral side to visualise the nasopharyngeal orifice of the ET. Subsequently, 15 microliters Evans blue solution, at a concentration of 20 mg/ml, were injected into the middle ear. The rat was returned to the supine position and the nasopharyngeal orifice of the ET was visualised under the microscope. The time between injection of the dye and the first appearance of the dye at the nasopharyngeal orifice of the ET was recorded as the DCT.

Statistical analysis

In a pilot study, the Po was increased immediately after the administration of normal saline into the middle ear (unpublished data). After three (or less) passive openings, the fluid could no longer be visualised otoscopically in the tympanic cavity and the Po returned to normal in all animals. Apparently, the ET must be opened a few times to perfuse the solution through the ET. Therefore the results of the first three measurements of Po and Pc were omitted. The means of the fourth, fifth and sixth Po and Pc were computed and used for the analyses in this study.

The Po, Pc and DCT were assumed to be normally distributed variables and analysed for means and standard errors of the mean (SEM). When both treatment groups were compared, means were analysed with the Student's t-test. When values before and after application of the surfactant or placebo were compared, the paired t-test was used. All data were analysed using the statistical package SPSS.

Results

The forced response test was performed successfully in all rats, while the dye clearance test failed in one rat due to technical problems. At baseline, no differences in weight and sex were found between the two groups.

Forced response test

Before the administration of surfactant or placebo, the Po as well as the Pc showed a wide variation between the rats. Some rats displayed low Po and Pc

(minimum 137 daPa and 25 daPa, respectively), while others were found to have high Po and Pc (maximum 330 daPa and 142 daPa, respectively). This interindividual variation was not related to weight or sex.

Figure 1 shows the mean Po and Pc (±2 SEM) before and after the administration of surfactant and placebo. At baseline, no substantial differences in Po and Pc were found between the two groups. Immediately after administration of the surfactant, the Po decreased significantly with 24 daPa (95% CI: 8-41 daPa), from 215 daPa to 191 daPa. This effect was still measured after 10 minutes. The effect of the surfactant on the Po was found to correlate with the baseline difference between the Po and Pc (Spearmann's correlation coefficient -0.75, p=0.01). In other words, the bigger the difference between the Po and Pc was before administration of the surfactant, the larger was the decrease of the Po. Placebo had no effect on the Po.

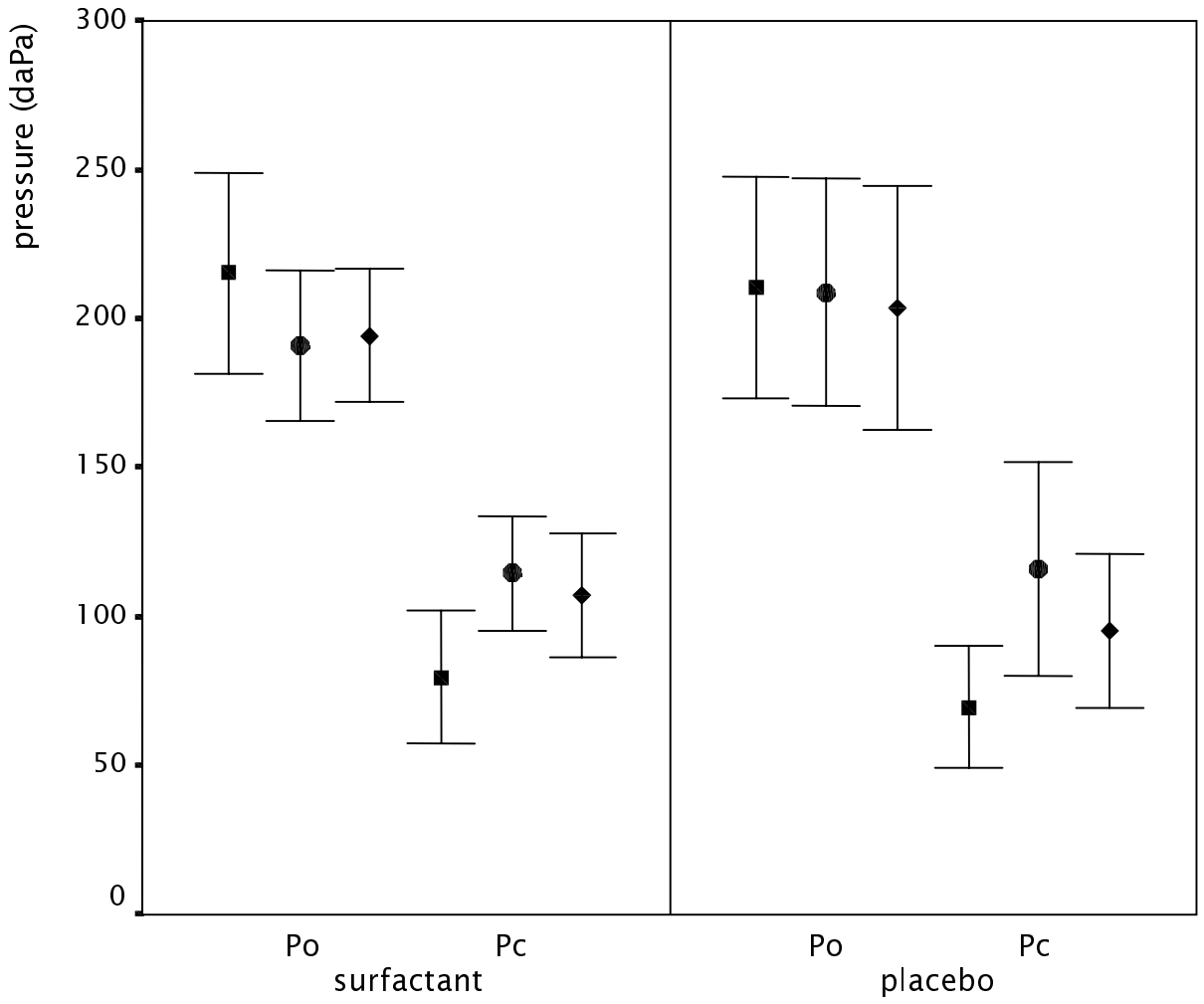

Figure 1. Mean opening (Po) and closing (Pc) pressures (± 2 SEM) before (solid square), immediately after (solid circle) and ten minutes after (solid diamond) administration of surfactant and placebo into the middle ear. (n=20)

In both groups a significant increase in Pc was found immediately after administration as shown in Figure 1. In the surfactant group, the Pc increased from 80 daPa to 115 daPa (difference 35 daPa, with 95% CI: 23-46 daPa), and in the placebo group, the Pc increased from 70 daPa to 116 daPa (difference 46 daPa, with 95% CI: 15-78 daPa). After ten minutes, the Pc was still significantly higher than the Pc before administration, but significantly lower than immediately after administration. No differences were found between the two groups.

Clearance test

In 6 of the 19 rats, the dye appeared at the nasopharyngeal orifice within 80 seconds. Three of these 6 rats received surfactant and had a mean DCT of 62 seconds (SEM 7 seconds). The other three received placebo and had a mean DCT of 75 seconds (SEM 5 seconds). This difference was not statistically significant (p=0.2).

In the remaining 13 rats, it took at least 20 minutes before the dye became visible. In these rats the DCT ranged from 20-43 minutes. The difference in mean DCT between the six rats that received surfactant (mean DCT 22.9 min., SEM 2.6 min.) and the seven rats that received placebo (mean DCT 28.1 min., SEM 3.2 min.) was not statistically significant (p=0.2). Based on the observed, vast difference in DCT, the rats were considered to represent two subgroups. The rats with a DCT ≤80 seconds were referred to as subgroup 1, while the rats with a DCT ≥20 minutes constituted subgroup 2.

The rats in subgroup 1 were comparable to the rats in subgroup 2 with regard to weight and sex. However, the baseline Po and Pc were significantly higher in subgroup 2 than in subgroup 1. The difference in mean Po was 68 daPa (95% CI: 30-106 daPa) and the difference in mean Pc was 38 daPa (95% CI: 15-61 daPa).

Discussion

ET surfactant is composed of a mixture of predominantly phospholipids, especially phosphatidylcholines and sphingomyelins.[18,19] Phospholipids are known to reduce the surface tension at an air-aqueous interface. However, since the ET is normally closed, the ET surfactant that covers the epithelium is supposed to act as a release agent by preventing solid-to-solid adhesion.[18]

Although the forced response test does not directly measure the physiological ability to actively open the ET, the test does provide useful information about the ET mechanics.[20-22] The Po is assumed to reflect the pressure which is needed to overcome all closing forces, including the solid-to-solid adhesion of the ET

walls (luminal forces) and the pressure of the cartilage and other surrounding tissues (extraluminal forces). The Pc is believed to reflect the extraluminal forces, while the difference between the Po and Pc is thought to reflect the luminal forces. In this study, administration of exogenous surfactant was found to reduce the Po. This effect was correlated with the baseline difference between the Po and the Pc. Rats with higher luminal forces at baseline showed a larger decrease in Po after the administration of surfactant, while all rats received the same amount and concentration of surfactant. Possibly, the concentration and/or composition of endogenous surfactant in the ET differs between rats resulting in variation in luminal forces. This variation may moderate the effect of exogenous surfactant. However, before any conclusions can be drawn, the properties of endogenous surfactant should be further revealed.

The Pc increased after administration of both surfactant and placebo. This increase in Pc may be caused by residual fluid in the ET. Immediately after passive opening of the ET, the pressure pump was turned off. Subsequently, the ET closed passively. However, residual fluid in the ET, may have obstructed the ET lumen just before actual closure of the ET, resulting in a higher Pc. This effect was diminished ten minutes later, probably because the residual fluid had been gradually cleared from the ET.

Clearance of the middle ear is established by the mucociliary transport and the pumping activity of the ET. By killing the animals, the pumping activity stops. However, the ciliary activity generally continues normally for several hours or even days after death.[23-25] Therefore, mucociliary transport can be measured immediately after exsanguination of the rats. In the studied population, contrasting results were found for the clearance test. In subgroup 1, the dye was visualised at the nasopharyngeal orifice within 80 seconds after injection into the tympanic cavity, while it took at least 20 minutes before the dye had passed the ET in subgroup 2. In other studies, mean DCTs of approximately 60 seconds were found in healthy rats and guinea pigs.[26-28] Therefore, we assume that for some reason a serious disturbance of the DCT was induced in subgroup 2.

In subgroup 1, no difference in DCT was found between surfactant and placebo. Others found that exogenous surfactant had a positive effect on mucociliary transport rate and ciliary beat frequency of frog palate and dog trachea.[16,17] Allegra et al.[16] studied frog palates (in vitro) sprayed with surfactant and found an increase in mucociliary transport rate of 16%. De Sanctis et al.[17] reported a fivefold increase in tracheal mucus velocity and a twofold increase in ciliary beat frequency in dogs treated with surfactant. These effects were ascribed to the anti-adhesive effects of surfactant. A reduction of the adhesion between the cilia

and the mucus blanket, may improve the effectiveness of this biological conveyor belt. The small number of rats in subgroup 1 may have been causative for the lack of a comparable effect in this study.
About the cause of the delay of the DCT in subgroup 2 can only be speculated. The baseline Po and Pc were significantly higher in subgroup 2 than in subgroup 1. This indicates that higher pressures were needed to open the ET and perfuse the solution, either surfactant or placebo, through the ET in these animals. The mucus blanket covering the ET epithelium is known to be a keyfactor in effective clearance and even small changes of this blanket may cause a disturbance of the mucociliary transport.[29,30] Forcing a solution through the ET may have caused such changes to the mucus blanket, resulting in a delay of the DCT. Possibly, rats with a high initial Po and Pc, i.e. with poor patency, are more susceptible to this kind of damage to the mucociliary system.
In conclusion, surfactant was found to decrease the closing forces of the ET in this as well as in other studies. No significant effect on the mucociliary clearance was found. Additional randomised, double-blind, placebo-controlled trials, should be conducted to determine the clinical relevance of these changes and to further assess the effect of surfactant on the ET function.

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Chapter 8

General discussion

The Eustachian tube and its functions have gained much scientific interest in the last decades, but still many questions are unanswered. Reason for this may be the lack of suitable tests to measure Eustachian tube function and/or the lack of perspectives for medical treatments to improve the Eustachian tube functions. This thesis describes a series of studies performed with the intention to provide greater insight into the Eustachian tube, especially related to measurement and improvement of its functions.

Measurement of the Eustachian tube function

This thesis *(Chapter 2)* showed that a reliable measure of the passive Eustachian tube ventilatory function in children is obtained by calculating the means of the first three measurements of the opening and closing pressures (forced response test). A single measurement of the pressure equilibration test, using wet swallowing and starting pressures of 100 and -100 daPa, is sufficient to determine active Eustachian tube ventilatory function. Unfortunately, the question remains which test provides the most useful and relevant information. It is yet unknown which test can be used best to discriminate between patients with various degrees of middle ear disease. The pressure equilibration test better imitates the normal physiological situation than the forced response test and therefore appears to be more relevant. On the other hand, the results of the forced response test are much more sensitive to variation than the categorised results of the pressure equilibration test.

No systematic differences were found between the left and the right ears *(Chapter 3)*. However, the intraindividual variation was very pronounced indicating that Eustachian tube ventilatory and protective function are more a characteristic of the individual ear than of the individual child even in case of bilateral otitis media with effusion (OME). Eustachian tube dysfunction seems to be a local process to a large extent and the contribution of each Eustachian tube to the development of OME in the corresponding ear is probably independent of the contralateral side. This finding questions the validity of trials on Eustachian tube function or middle ear disease that use the opposite ear as a control (split level design). The test results of one Eustachian tube should not be extrapolated to the other Eustachian tube and the use of the opposite ear as a paired control is discouraged.

A limitation of the studies on humans described in this thesis is that they only included children with ventilation tubes. It would be very interesting to study the Eustachian tube function in otologically healthy children in order to determine

the natural course of the Eustachian tube function (if possible in relation with the development of OME) and to gain knowledge about the differences in Eustachian tube function between healthy and diseased ears. However, a prerequisite for the tests as they are performed in this thesis is an open tympanic membrane (i.e. with a ventilation tube or a perforation). Other investigators performed the forced response test and the pressure equilibration test with an intact tympanic membrane as well, but in those cases a pressure chamber was needed to indirectly change the pressure in the middle ear cavity.[1] The use of a pressure chamber has, however, evident practical limitations, especially for children. An alternative test method in cases with an intact tympanic membrane may be sonotubometry. Sonotubometry is based on the conduction of sound waves through the Eustachian tube if the tube opens during, for example, swallowing. Sound waves are applied to the nasopharynx through one of the nostrils. A microphone is connected to the external ear canal. An increase in the sound pressure level in the ear canal during swallowing is assumed to indicate active opening of the Eustachian tube.[2] Although this method is safe and patient-friendly, its usefulness and reliability remain debatable.[3,4] In addition, the test method only provides information about the active Eustachian tube function, like the pressure equilibration test, but does not measure passive Eustachian tube opening. Yet we recommend to study the merits of sonotubometry for the evaluation of Eustachian tube function.

The Eustachian tube has three functions with respect to the middle ear: ventilation, protection and clearance. Most studies investigate only one of these three functions. We investigated both the ventilatory and the protective function in children. Unfortunately we were not able to study the clearance function in these children. In vivo measurement of the clearance function in children is difficult, if not impossible, due to the practical and ethical objections of injecting contrast medium into the middle ear. As a result, measurement of the clearance function remains confined to animal studies. Yet it is important to learn how much the three Eustachian tube functions are interrelated and interdependent, and to what extent they vary between different children.

Improvement of the Eustachian tube function

A comprehensive summary of the English language literature on therapeutic improvement of Eustachian tube function *(Chapter 4)* showed that most studies concerned the effect of interventions on the Eustachian tube ventilatory function. In addition, there was wide variation in the type of interventions, test methods and study populations and most studies were underpowered and not placebo-

controlled. Despite these restrictions, the results indicated that there may be several potential interventions to improve Eustachian tube function. Surfactants, beta adrenoceptor agonists and decongestants are suggestive to have a positive effect on passive Eustachian tube function and roxythromycin may enhance the clearance capacity.

The insertion of ventilation tubes, which are widely applied to aerate the middle ear in children with OME, did not result in an improvement of the Eustachian tube ventilatory function in children with OME during the first three months after surgery *(Chapter 5)*.This lead to the conclusion that the poor Eustachian tube function in these children is more likely to be a causal factor of OME than a result of the disease. Certain children may have poor Eustachian tube ventilatory function, which makes them more susceptible to OME.

Nasal decongestants are frequently recommended for the treatment of OME. The rationale behind this treatment strategy is that these drugs decongest the mucosa of the Eustachian tube, thus improving the Eustachian tube function. However, a randomised, double-blind, placebo-controlled study that is described in this thesis *(Chapter 6)* showed that a relatively large dose 0.05% xylometazoline hydrochloride nose drops did not improve the Eustachian tube ventilatory or protective function in children with ventilation tubes due to persistent OME. Several explanations emerge, the decongestant did not sufficiently reach the Eustachian tube mucosa or the decongestive effect was too small to result in an improvement of the Eustachian tube function in these children.

Since surfactant is secreted by the Eustachian tube epithelium and is assumed to enable normal functioning of the Eustachian tube,[5,6] we described the effect of exogenous surfactant on the Eustachian tube function in a small group of otologically healthy rats *(Chapter 7)*. Exogenous surfactant was found to decrease the closing forces of the Eustachian tube in otologically healthy rats. Surprisingly, no significant effect on the mucociliary clearance was found, but replicate studies are needed. Nevertheless, the administration of exogenous surfactant could be a promising intervention to improve Eustachian tube function. It is, however, premature to recommend the use of surfactant in humans, because the (relevance of the) effects of exogenous surfactant should be studied in more detail first.

Whenever interventions to improve the Eustachian tube function are developed and studied, one should consider that such an intervention preferably improves all three Eustachian tube functions, but at least not positively affects one

function and, at the same time, negatively affects another. Moreover, it should be reckoned with that certain interventions may be effective in some children, while other children do not benefit from them at all. Once an intervention is proven to be effective to improve the Eustachian tube function, the question remains as to whether this improvement is of clinical significance for the individual patient. The most critical issue in this context is the question whether an improvement of the Eustachian tube function will result in prevention or resolution of OME. Although there is no dispute about the Eustachian tube being important, it remains unclear to what extent impairment of the different Eustachian tube functions contributes to the development of OME. In particular, the degree and importance of impairment of the protective and clearance function remain unravelled.

Eustachian tube dysfunction is not the only factor involved in the development of OME. Impairment of the systemic immunological responses to pathogens is also assumed to be important in the aetiology of OME.[7-10] Together, Eustachian tube dysfunction and an impaired immune response are assumed to co-operate and interact in the development of OME.[11] Nonetheless, distinct differences may exist in the extent to which those factors contribute to the aetiology of OME within different children. In one child the Eustachian tube dysfunction may be prominent, while in another child an impaired immune response may be more pronounced.

Recommendations for future research

Although the studies described in this thesis substantially add to the knowledge about the Eustachian tube and its functions, many questions are still to be unravelled.

The differences in Eustachian tube dysfunction should be studied in children with different degrees of OME to describe the natural course of the Eustachian tube dysfunction in these children. This may reveal why some suffer from recurrent or persistent OME, while others have only transient OME. In addition, such studies may show whether the Eustachian tube function tests can be used to discriminate between these groups of children and to determine which children should receive medical treatment.

The usefulness of the forced response test and the pressure equilibration test in clinical practice also needs to be studied. Patients with chronic Eustachian tube dysfunction are often treated with long-term ventilation tubes. These ventilation tubes should replace the Eustachian tube ventilatory function until the

Eustachian tube function is normalised. The forced response test and the pressure equilibration test may be used to reliably measure whether the Eustachian tube function is normalised. In other words, they may be used to establish whether aeration of the middle ear by the Eustachian tube is expected to be normal to justify the decision to remove the ventilation tubes.
The reliability and applicability of sonotubometry should be tested. If sonotubometry proves to be useful, this method may be used to study the Eustachian tube ventilatory function in cases with intact tympanic membranes in a research setting.
The importance of impairment of the Eustachian tube functions, especially the protective and clearance function, in the development of OME should be studied in more detail. Preferably, such studies should combine the role of Eustachian tube dysfunction with the role of impairment of the immune response, since both factors are assumed to be core elements in the development of OME.
Based on the positive effect on the Eustachian tube ventilatory function in rats in our and other studies,[12,13] the improvement of the mucociliary transport[14,15] and the positive effect of exogenous surfactant on experimentally induced OME in gerbils,[16] the administration of exogenous surfactant could be a promising intervention to improve Eustachian tube function. The role of surfactant in normal Eustachian tube function, therefore, requires more research. Studies on the therapeutic value of surfactant for treatment of OME should be performed both in animal models as well as in humans.

Implications for clinical practice

Although the forced response test and the pressure equilibration test were found to provide reliable results, their use in clinical practice will remain postponed until they are proven to be useful to discriminate between different degrees of OME and Eustachian tube dysfunction.
No intervention is available yet of which the application in clinical practice is justified based on the present scientific knowledge.

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Summary

In *Chapter 1*, the current concept of the Eustachian tube (ET) and its functions with respect to the middle ear is described. The ET connects the middle ear with the nasopharynx and is very important with respect to the middle ear. Frequent active opening of the ET allows pressure equilibration between the middle ear and ambient air (ventilatory function). The normally closed ET protects the middle ear from ascending secretions and micro-organisms, as well as from nasopharyngeal pressure variations (protective function). The mucociliary epithelium of the ET is involved in local defence against pathogens and is concerned with clearance of secretions and debris from the middle ear towards the nasopharynx (clearance function). The objective of this thesis was to add to the scientific knowledge of the ET, more specific:

-to study the measurement conditions (i.e. type and number of tests, unilateral or bilateral measurement) for obtaining a reliable measure of the Eustachian tube function;
-to study the effect of common (e.g. ventilation tubes, nasal decongestants) and promising (e.g. surfactant) interventions on the Eustachian tube function.

In *Chapter 2*, the reliability of the forced response test and the pressure equilibration test is described. We showed that a reliable measure of the ET ventilatory function is obtained by taking the mean of the first three measurements of the opening and closing pressures to characterise passive ET ventilatory function (forced response test). A single measurement using wet swallowing and starting pressures of 100 and -100 daPa is sufficient to determine active ET ventilatory function (pressure equilibration test).

In *Chapter 3*, the differences in function between the left and right ET in children with bilateral otitis media with effusion (OME) are described. Although no systematic differences were found between the left and the right ears, the intraindividual variation was very pronounced. This indicates that ET function is much more a characteristic of the individual ear than of the individual child. These findings question the validity of trials on ET function or middle ear disease that use the opposite ear as a control (split level design).

In *Chapter 4*, a comprehensive summary of the different studies that described interventions to improve ET function is given. Despite several restrictions of the reviewed studies (e.g. different test methods were used, studies were not placebo-controlled), the results of this review indicate that the ET function may

be improved by medical intervention. Several drugs (surfactants, beta adrenoceptor agonists and decongestants) were shown to have an effect on passive ET function, while roxythromycin enhanced the clearance function. Nonetheless, it is still premature to recommend any of these interventions to improve ET function in humans.

In *Chapter 5*, the effect of ventilation tubes on the ET function in children with OME is reported. The insertion of ventilation tubes did not improve the ET ventilatory function. Therefore, the poor ET ventilatory function in these children is more likely to be a causal factor of OME instead of being a result of the inflammation of the middle ear and the accumulation of fluid. Certain children may have poor intrinsic ET function, which makes them more susceptible to OME.

In *Chapter 6*, the results of a randomised, double-blind, placebo-controlled study on the effect of a nasal decongestant on the ET ventilatory and protective function in children with ventilation tubes is outlined. These results showed that a relatively high dose of xylometazoline nose drops, administered with the child in supine position, had no effect on the ventilatory or the protective function of the ET in this group of children. So the widespread use of decongestant nose drops to improve the ET function in this group of children seems not justified.

In *Chapter 7*, the effect of exogenous surfactant on the ventilatory and clearance function of the ET of otologically healthy rats is described. Administration of exogenous surfactant into the middle ear caused a significant decrease in the closing forces of the ET (i.e. opening pressure) even in these otologically healthy rats. No significant effect on the mucociliary clearance was found. Additional studies should be conducted to further assess the effect of surfactant on the ET function.

In *Chapter 8*, the overall conclusions of this thesis are discussed in the light of the present knowledge of ET (dys)function. It is noted that the studies on humans described in this thesis only included children with ventilation tubes. It would be interesting to study the ET function in otologically healthy children as well in order to determine the natural course of the ET function and to gain knowledge about the differences in ET function between healthy and diseased ears. In such studies, the clearance function should be studied as well. It is also noted that no intervention has sufficiently been proven effective in improving ET

function to be applied in clinical practice. Exogenous surfactant seems to be the most promising intervention to improve ET function, but this should be studied in more detail first. Finally, it is considered to be important to learn how much the three ET functions (i.e. ventilation, protection and clearance) are interrelated and interdependent, and to what extent they contribute to the development of OME. Preferably, such studies should combine the role of ET dysfunction with the role of impairment of the immune response.

Samenvatting

Meer dan 2500 jaar geleden werd door Alcmaeon van Sparta reeds aangenomen dat het oor en de bovenste luchtwegen met elkaar verbonden zijn. In 1562 werd deze open verbinding tussen het middenoor en de keelholte vernoemd naar de Italiaanse anatoom Bartholomeus Eustachius, die de buis van Eustachius in detail beschreef in zijn "Epistola de Auditus Organis". Onderzoek in de daarop volgende eeuwen heeft duidelijk gemaakt dat de buis van Eustachius een aantal belangrijke functies heeft, te weten ventilatie, bescherming en klaring van het middenoor.
In rust is de buis van Eustachius gesloten, maar tijdens slikken, gapen of bewegen van de onderkaak gaat hij open. Deze actieve opening van de buis van Eustachius zorgt voor beluchting van het middenoor, zodat de luchtdruk in het middenoor gelijk is aan de buitendruk (ventilatiefunctie). Met uitzondering van deze kortdurende actieve opening is de buis van Eustachius echter gesloten om het middenoor te beschermen tegen secreties en micro-organismen uit de keelholte. Tevens beschermt de gesloten buis van Eustachius het middenoor tegen drukschommeling in de keelholte (beschermingsfunctie). Het mucociliaire epitheel van de buis van Eustachius zorgt voor het afvoeren van secreties en debris uit het middenoor naar de keelholte en speelt een belangrijke rol bij de lokale afweer tegen pathogenen (klaringsfunctie).
Het doel van de studies beschreven in dit proefschrift is om meer inzicht te verkrijgen in de buis van Eustachius en zijn functies, met name in het meten en verbeteren ervan.

De betrouwbaarheid van de forced response test en de pressure equilibration test wordt beschreven in *Hoofdstuk 2*. Beide testen worden gebruikt om de ventilatiefunctie van de buis van Eustachius te meten. De forced response test meet de minimale druk die nodig is om de buis van Eustachius open te blazen (openingsdruk) en de druk waarbij de buis van Eustachius spontaan weer sluit na deze passieve opening (sluitingsdruk). Beide drukken karakteriseren de passieve ventilatiefunctie. Met de pressure equilibration test wordt de actieve ventilatiefunctie gemeten, m.a.w. het vermogen om een verschil tussen de druk in het middenoor en de buitendruk te equilibreren middels actieve opening van de buis van Eustachius (bv. door te slikken).
Om een betrouwbaar resultaat van de forced response test te verkrijgen, bleek het nodig het gemiddelde van de eerste drie metingen van de openings- en sluitingsdruk te nemen. Het resultaat van de pressure equilibration test bleek betrouwbaar indien de meting eenmalig werd verricht met het gebruik van "wet

swallowing" (d.w.z. het drinken van wat water) en startdrukken van 100 en -100 decapascal.

In *Hoofdstuk 3* worden de forced response test en de pressure equilibration test gebruikt om de verschillen in ventilatiefunctie te beschrijven tussen de linker en rechter buis van Eustachius van kinderen met bilaterale otitis media met effusie. Tevens wordt met behulp van de sniff test het verschil in beschermingsfunctie bestudeerd. Met de sniff test wordt gemeten of het krachtig ophalen van de neus leidt tot het ontstaan van een negatieve druk in het middenoor. Indien dat het geval is, is er sprake van een matig tot slechte beschermingsfunctie. Hoewel er geen systematische verschillen gevonden werden tussen links en rechts, waren bij veel kinderen de openings- en sluitingsdruk van de linker en rechter buis van Eustachius niet aan elkaar gelijk. Sterker nog, de verschillen in openings- en sluitingsdruk tussen links en rechts (de intra-individuele variatie) waren vrijwel net zo groot als de verschillen in deze drukken tussen verschillende kinderen (de inter-individuele variatie). Ook het resultaat van de pressure equilibration test en de sniff test was bij ongeveer éénderde van de kinderen verschillend voor de linker en rechter buis van Eustachius. Het functioneren van de buis van Eustachius lijkt meer een specifieke eigenschap van de betreffende buis te zijn dan van het kind. De buis van Eustachius functie aan de ene kant is niet representatief voor de functie aan de andere kant. Deze bevindingen plaatsen vraagtekens bij de validiteit van studies naar de buis van Eustachius functie of middenoorziekten, die het contralaterale oor als controle oor gebruiken (split level design).

De veronderstelling dat een verminderde buis van Eustachius functie een rol speelt bij het ontstaan van vocht achter het trommelvlies heeft verscheidene onderzoekers ertoe aangezet te bestuderen op welke wijze de buis van Eustachius functie positief beïnvloed kan worden. In *Hoofdstuk 4* wordt een samenvatting gegeven van deze studies. In een aantal opzichten bleken de studies verschillend. Er werden verschillende testmethoden gebruikt om de buis van Eustachius functie te meten. De onderzoekspopulaties varieerden en waren veelal zo klein dat alleen een groot effect aangetoond kon worden. Bovendien werd bij de meeste studies niet gecontroleerd op placebo-effecten. Tevens werd in slechts een paar studies het effect op de beschermings- en klaringsfunctie beschreven. Ondanks deze beperkingen kon uit dit literatuuroverzicht toch geconcludeerd worden dat verschillende farmaca potentieel effectief zijn om de buis van Eustachius functie te verbeteren. Surfactant, beta adrenoceptor

agonisten en decongestiva bleken een positief effect op de passieve ventilatiefunctie te hebben. Roxythromycine verbeterde de klaringsfunctie. Er is echter nog onvoldoende wetenschappelijk bewijs om een van deze interventies in de klinische praktijk toe te passen.

Vrijwel alle kinderen maken voor het vijfde levensjaar minstens één periode van otitis media met effusie door. Indien de effusie langer dan drie maanden blijft bestaan, worden in veel gevallen trommelvliesbuisjes geplaatst. Trommelvliesbuisjes nemen de functie van de buis van Eustachius over doordat ze zorgen voor het afvoeren van de effusie en het beluchten van het middenoor. Of het plaatsen van trommelvliesbuisjes ook direct effect heeft op de buis van Eustachius functie is nog altijd controversieel. Het effect van trommelvliesbuisjes op de buis van Eustachius functie bij kinderen met otitis media met effusie werd daarom bestudeerd en beschreven in *Hoofdstuk 5*.
Het plaatsen van trommelvliesbuisjes en de daarop volgende beluchting van het middenoor leidde niet tot een verbetering van de ventilatiefunctie van de buis van Eustachius. De matige buis van Eustachius functie bij deze kinderen is dan ook waarschijnlijk niet een gevolg van de otitis media met effusie, maar juist één van de oorzaken. Sommige kinderen zijn mogelijk gevoeliger voor het krijgen van otitis media met effusie, omdat bij hen de buis van Eustachius matig tot slecht functioneert.

In *Hoofdstuk 6* wordt het effect beschreven van xylometazoline neusdruppels, een lokaal decongestivum, op de ventilatie- en beschermingsfunctie van de buis van Eustachius bij kinderen met trommelvliesbuisjes. Lokale decongestiva worden op grote schaal toegepast ter voorkoming en behandeling van otitis media met effusie. De ratio achter deze behandeling is dat deze geneesmiddelen via decongestie van het slijmvlies een verbetering van de buis van Eustachius functie tot gevolg zouden hebben. Voor deze hypothese is echter onvoldoende bewijs beschikbaar.
De buis van Eustachius functie werd gemeten voor en na toediening van vijf druppels xylometazoline of placebo-oplossing. De druppels werden toegediend terwijl het kind op de rug lag met het hoofd iets naar de ipsilaterale zijde gedraaid om de expositie van de buis van Eustachius aan de druppels te optimaliseren. De resultaten toonden aan dat xylometazoline neusdruppels geen effect hebben op de genoemde functies van de buis van Eustachius. Bij deze groep kinderen dienen lokale decongestiva dan ook niet gebruikt te worden ter verbetering van de buis van Eustachius functie.

Het effect van exogeen surfactant op de ventilatie- en klaringsfunctie van de buis van Eustachius van otologisch gezonde ratten wordt beschreven in *Hoofdstuk 7*. Endogeen surfactant wordt geproduceerd en uitgescheiden door het epitheel van de buis van Eustachius. Surfactant heeft een oppervlaktespanning verlagende werking en speelt mogelijk ook een rol bij de afweer tegen pathogenen. Aangenomen wordt dat surfactant nodig is voor het normaal functioneren van de buis van Eustachius.
Bij gezonde ratten veroorzaakte toediening van surfactant in het middenoor een significante afname van de druk die nodig is om de buis van Eustachius open te blazen. Er werd geen effect op de klaringsfunctie aangetoond. Nog te verrichten gerandomiseerde, dubbelblinde, placebogecontroleerde trials zijn nodig om uit te wijzen wat de klinische relevantie is van deze veranderingen en om het effect van exogeen surfactant verder in kaart te brengen.

In *Hoofdstuk 8* worden de conclusies van dit proefschrift besproken in het licht van de huidige wetenschappelijke kennis van de buis van Eustachius en zijn functies. Allereerst lijkt het een beperking van de studies in dit proefschrift dat de buis van Eustachius functie alleen gemeten werd bij kinderen met trommelvliesbuisjes. Het zou interessant zijn om ook bij otologisch gezonde kinderen de verschillende buis van Eustachius functies, dus inclusief de vooralsnog weinig onderzochte klaringsfunctie, te meten om zodoende het natuurlijk beloop van deze functies te bepalen en inzicht te verkrijgen in de verschillen tussen gezonde en zieke oren. Ten tweede wordt opgemerkt dat geen enkele interventie reeds voldoende effectief is gebleken in het verbeteren van de buis van Eustachius functie om toegepast te worden in de klinische praktijk. Exogeen surfactant lijkt de meestbelovende interventie, maar dat dient eerst verder onderzocht te worden. Tenslotte wordt vastgesteld dat het belangrijk is om te weten in hoeverre de drie afzonderlijke buis van Eustachius functies onderling samenhangen en afhankelijk zijn van elkaar. Tevens dient verder onderzocht te worden in welke mate deze verschillende functies bijdragen aan de pathogenese van otitis media met effusie. Bij voorkeur wordt in dergelijke studies naast de rol van buis van Eustachius dysfunctie tegelijkertijd de rol van een verminderde afweer onderzocht omdat een verminderde afweer vermoedelijk ook een belangrijke rol speelt bij het ontstaan van otitis media met effusie.

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Curriculum Vitae

Niels van Heerbeek werd op 20 september 1974 geboren in Tilburg. Na het doorlopen van de lagere en middelbare school, behaalde hij in 1992 het diploma Gymnasium β aan het St. Odulphus lyceum in Tilburg. In datzelfde jaar begon hij zijn studie geneeskunde aan de Rijks Universiteit Leiden. Na het behalen van zijn propaedeuse vervolgde hij zijn studie aan de Katholieke Universiteit Nijmegen. Als afsluiting van zijn co-schappen werkte hij in een districts ziekenhuis in Tanzania en kort daarna behaalde hij zijn artsexamen. Na zijn artsexamen in 1999 werd hij aan de afdeling keel-, neus- en oorheelkunde van het (toen nog) Academisch Ziekenhuis Nijmegen St. Radboud aangesteld als arts-onderzoeker om de meetbaarheid van de buis van Eustachius functie te onderzoeken bij kinderen. Een aantal maanden later kreeg dit onderzoek een vervolg en werd hij aangesteld als assistent-geneeskundige in opleiding tot klinisch onderzoeker (AGIKO). Samen met een aantal andere onderzoekers werd hij verantwoordelijk voor de KNOOP 4 studie, een studie naar recidiverende otitis media met effusie bij kinderen. Deze studie zal naar verwachting in 2004 afgerond worden. Inmiddels is hij begonnen aan de opleiding tot keel-, neus- en oorarts, die hij vermoedelijk zal afronden in 2006.

Sinds december 1999 is Niels actief betrokken bij Stichting Eardrop. Stichting Eardrop zendt jaarlijks teams van specialisten naar Kenia om aldaar dove en slechthorende kinderen te opereren, lokale artsen op te leiden in de oorchirurgie en medewerkers van dovenscholen te trainen en begeleiden in hun zorg voor dove en slechthorende kinderen.

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