Novel approaches to performance assessment of heat and moisture exchangers for pulmonary protection and rehabilitation in laryngectomized patients

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Chapter 8

General discussion and future perspectives
DISCUSSION AND FUTURE PERSPECTIVES

Previous clinical research has provided sound knowledge about the effects of heat and moisture exchangers on clinical pulmonary functioning, clinical symptoms, and intra-tracheal climate changes in laryngectomized patients.\textsuperscript{1-9} The aim of this thesis was to further enhance our understanding of how an HME device functions, to develop new techniques to assess the humidification effect of an HME and to determine the HME effects on mucociliary clearance and pulmonary infections.

A newly developed, straightforward and universally applicable ex vivo method that measures the HME water exchange performance, was introduced and validated in chapter 2 and 3. This method assesses the HME weight at the end of inspiration and at the end of expiration, and thus, directly measures the amount of water conserved by the HME during a breathing cycle.

This newly developed method has made it possible to carry out water exchange measurements in a large series of different HME types within an acceptable time window (chapter 4). A wide range of water exchange and humidity performances was found in the 23 evaluated devices. Also, this method helped us to understand the role of hygroscopic salt (impregnated in the core material of most HMEs to enhance their efficiency) in hygroscopic HME devices (chapter 4). We have found that the total water uptake of a hygroscopic HME during breathing is related to its humidity and water exchange performance.

This knowledge was the basis of chapter 5, where the total water uptake capacity was used to determine whether hygroscopic HME devices used by laryngectomized patients still function optimally after 24-hour tracheostoma application. Loss of water uptake capacity (and therefore loss of hygroscopic salt) was found in the three tested HME types used by 10 patients. However this loss was only significant for the device type with the highest initial water uptake of the three. The remaining water uptake of all three types was still clinically acceptable. This study validates the advice (based on microbiological considerations) to change an HME every 24 hours from the point of view of humidity performance.

The effect on mucociliary clearance and pulmonary infections of HME use was assessed in chapter 6 and 7. In chapter 6, long- and short-term effects of HME
stoma application was determined using scintigraphy for tracheal mucus transport velocity and tracheal epithelial brush biopsies for evaluation of ciliated cells in non-HME users and HME users. The tracheal epithelium of long-term HME users contains significantly more ciliated cells than in long-term non-HME users. The number of ciliated cells near the stoma is significantly lower than more distal in the trachea in both the non-HME users and HME users. The tracheal mucus transport velocity was not significantly higher (better) in long-term HME users than in non-HME users and is comparable to patients with a chronic lung disease like asthma or COPD.\textsuperscript{10-12} Removal (1 hour) of an HME in HME users did not show a significant effect on mucus transport velocity. Chapter 7 gives more insight in the incidence of pulmonary infections in laryngectomized patients and shows a tendency that the number of tracheobronchitis and pneumonia episodes is lower in HME users than in non-HME users based on a retrospective clinical study and a European wide survey among Head and Neck surgeons. The assumption by experienced head and neck surgeons that wintertime tracheobronchitis with severe crusting has become much less prominent since the introduction of HMEs, seems valid.

**OVERVIEW OF DIFFERENT APPROACHES TO ASSES THE EFFECT OF AN HME**

Many different methods are now available to assess different aspects of (possible) HME effects in laryngectomized patients; Table 1 shows a non-exhaustive overview. As mentioned in the introduction, the immediate climate change caused by an HME is followed by a chain of different physiological changes at different time scales, which is important to keep in mind when designing a study. For example, mucus transport velocity and ciliated cells (mucociliary clearance) need time to recover from the climate changes caused by the laryngectomy (weeks to months). The HME effects on incidence of pulmonary infections (and possibly pulmonary function) can only be observed after long-term use of HMEs.
Table 1. Overview of different approaches used to determine the effect of using an HME for laryngectomized patients. For advantages, disadvantages, and limitations see Table 2.

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<tr>
<td>Humidity</td>
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<td>Ex vivo Ex vivo air humidity changes</td>
<td>This thesis, chapter 2, 3, 4 13-15</td>
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<tr>
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<td>Weighing method</td>
<td>Ex vivo Weight change (water exchange) in humid conditions</td>
<td>This thesis, chapter 2, 3, 4 13-15</td>
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<tr>
<td>Water uptake</td>
<td>Weighing</td>
<td>In vitro The amount of HME weight increase during breathing</td>
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<tr>
<td>Water loss</td>
<td>ISO 9360-2:2001 (weighing)</td>
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<td>Resistance</td>
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<td>Ciliated epithelium</td>
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<td>Clinical outcome* Score of experienced complaints by patients</td>
<td>This thesis, chapter 3 and 6 1,4,7,14,26</td>
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<td></td>
<td>- Tally sheets</td>
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<td></td>
<td></td>
<td>Clinical outcome* Quality of life</td>
<td>2</td>
</tr>
<tr>
<td>Pulmonary infections</td>
<td>- Questionnaires</td>
<td>Clinical outcome* Number of clinical diagnosis, antibiotic prescription, mortality rate, hospital admission</td>
<td>This thesis, chapter 7 27</td>
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<td></td>
<td>- Medical records</td>
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<td></td>
<td>- Survey</td>
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</table>

N/A = not applicable
* Clinical outcome is the HME effect observed in/experienced by patients
In the following paragraphs, the pros and cons of the various assessment methods will be discussed.

**Intra tracheal humidity and temperature (ACE)**

A heat and moisture exchanger device, as its name implicates, has a beneficial effect on heat and moisture climate in the trachea. Measuring climate changes in vivo is a fundamental approach to study the effect of an HME, but is complicated and technically challenging as a very fast humidity sensor is required and condensation must be avoided completely if valid results are to be obtained. Zuur et al have developed the ACE (Airway Climate Explorer) for this purpose. And although the various studies carried out have greatly increased the knowledge of postlaryngectomy climate changes in the trachea and the HME effects on those, a pitfall is that the measurements are very sensitive to location of probe insertion in the trachea (which is difficult to control) as the first part of the trachea acts as an efficient HME as well. Measurements with the ACE constitute a burden on patients and comparison of many different devices is hardly ethically justified in patients.

**Ex-vivo humidity**

Ex vivo humidity determination is simpler to perform than intra-tracheal humidity (no condensation problems, even if a very fast humidity sensor is still required), and has been shown to be a valid measure of HME performance (chapter 2, 3 and 4). The ex vivo fast humidity measurements were used as an intermediate step to compare the water exchange with the available data on in vivo intra-tracheal end-inspirational absolute humidity. Although in the test set-up in this thesis breathing was performed by a healthy volunteer, in future also a laryngectomized patient could be used as the ‘breathing source’.

**Water exchange (weighing method)**

The newly developed weighing method (measuring the water exchange of an HME during the breathing cycle), introduced in chapter 2 and further validated in chapter 3 and 4, is a simple and straightforward technique, is universal applicable and uses human expiratory air water saturation values. The study has used mouth breathing by a healthy volunteer instead of stoma breathing by a laryngectomized patient,
but expiratory humidity levels are in both cases almost completely saturated with water at body temperature \(^{29,30}\), and therefore no large differences in outcome are expected. Also it was shown that the results are volunteer independent (chapter 2), and it would be possible to use the weighing method with laryngectomized patients as well.

\textit{Water uptake (hygroscopic salt)}

Water uptake capacity of a hygroscopic HME can be simply determined by weighing the HME after conditioning at a range of ambient humidities (chapter 4). Water uptake was used to measure performance of HMEs used by patients (chapter 5). This method is only applicable for hygroscopic HMEs, and is an indirect measure for humidity/water exchange performance with the limitation that only the effect of the hygroscopic salt is measured and not the contribution of the case and the foam itself.

\textit{Water loss (ISO)}

The in vitro method (ISO 9360-2:2000/2001)\(^{17,18}\) measures the effect of reducing the total amount of water loss (weight loss) by using an HME in a mechanic lung model during 24 hours. The ISO standards ought to be universally applicable, but it has pitfalls in calibration that lead to a wide range of acceptable outcome values. Also, as described in chapter 2, the ISO expiratory air saturation does not seem to be entirely representative for expiratory human lung air saturation. This might be due to difference in dead space between the ISO test configuration and human lungs, but this discrepancy has not been fully understood yet. ISO should yield a universally available measure of HME performance for medical professionals to enable them to compare (humidity) performance between the available HME types, but the ISO water loss values are only available (provided by the manufacturer) for a few HME types. Unfortunately most manufacturers were unable or unwilling to provide the ISO data (chapter 4).

\textit{Resistance}

The ISO standard 9360-2:2001\(^{18}\) provides a pressure drop outcome as measure for airflow resistance of an HME using completely dry air. These values are given for
some of the devices used in chapter 2, 3 and 4. A few studies have assessed airflow resistance in some of the available devices for laryngectomized patients.\textsuperscript{18-21} It has been show that patients experience (subjective) differences in airflow resistance using the same HME, and that higher subjective resistance is related to decreased compliance.\textsuperscript{25, 31, 32} When converting pressure drop to resistance, it is important to use the proper (quadratic) relationship between pressure and flow.\textsuperscript{20}

**Lung function**

It has been hypothesized that the HME increases the extra-thoracic expiratory breathing resistance (like pursed lip breathing in COPD patients)\textsuperscript{10-12}, which might be instantaneously beneficial for arterial oxygenation levels in laryngectomized patients. However, a careful randomized crossover study could not confirm a beneficial effect on tcpO\textsubscript{2} of using an HME, using a percutaneous oxygenation measurement.\textsuperscript{23} Long-term evaluation of the effect of an HME using pulmonary function tests have resulted in different spirometric outcome values in laryngectomized patients\textsuperscript{3, 25, 31}, but only in one study a beneficial influence on inspiratory values was found after three months.\textsuperscript{3} The intra-individual variance of pulmonary function parameters might be too large to measure such an HME effect more consistently. Alternatively, the length of the study period might not have been sufficient to find possible late HME effects on lung function.\textsuperscript{23, 33}

**Tracheal mucus transport velocity**

Scintigraphy is an objective approach of measuring the mucus transport velocity (\textsuperscript{11,34} and chapter 6). However, a limitation of this method is that the performance of consecutive scans has a time window of at least 24 hours due to the radioactivity. In chapter 6 we have found a large intra- and interpatient variability in mucus transport rates similar to previous studies. Together with the limited available number of patients, this makes it difficult to find significant differences between HME and non-HME use.\textsuperscript{11,35,36}

**Ciliated epithelium**

Ciliated epithelium can be assessed using ciliary brush biopsies. Number of ciliated cells, ciliary movement, ciliary coordination and ciliary beat frequency are possible
outcome values. The number of ciliated cells seems a fair measure for the state of ciliated epithelium, as we found consistent results in chapter 6 (e.g. more ciliated cells intra-tracheally than near the stoma). The finding that there were no differences measured in the fraction of moving or coordinating ciliated cell strips between HME and non-HME users (chapter 6) might be an artifact. The in vitro environment (optimal immersion in cell medium) is not similar to the in vivo intra-tracheal environment after TLE, where relatively dry and cold air is passing the epithelium. It is also possible that the fraction of moving or coordinating ciliated cells, which has mostly been used to map primary ciliary damage, is not well suited to map secondary ciliary damage. Ciliary beat frequency (CBF) is another score that is used in primary ciliary damage, but decreased CBF is not always present in secondary ciliary damage and therefore not used in chapter 6.

Brush biopsies can damage the epithelium, which means that repetition of brush biopsies should be performed 2-3 weeks to minimize the effect of iatrogenic damage by the method.

Clinical complaints

Pulmonary complaints (such as coughing and forced mucus expectoration) and quality of life are often assessed with the use of validated and/or study-specific questionnaires and/or tally sheets. Such assessments of patients’ experience before and after the use of an HME have proven to provide important, and relevant clinical parameters. However, these outcome parameters still are subjective, and thus, should be interpreted with care, no matter how well-validated the questionnaires are.

Pulmonary infections

Retrospective medical record studies often have the drawback of showing a documentation bias, as indeed was the case in our study (chapter 7), especially in the early years of the scoring period (starting from 1973). Prospective scoring of pre-defined pulmonary infections obviously is more reliable, but when there is a limited time window (like the 6 months in Jones et al), the incidence will probably be underestimated. Using a survey to estimate the effect of HMEs on pulmonary infections and treatment is of course dependent on the response rate and on the
‘quality’ of the responders. For an expert’s opinion, sufficient experience with laryngectomized patients, both non-HME and HME users, is needed. Retrospective data study and survey questionnaire results have not the highest level of evidence, however the combination of these results (chapter 7), especially when the outcomes point in the same direction, gives more insight in the incidence of pulmonary infections and treatment in laryngectomized patients and the beneficial clinical effect of an HME, which has an impact on medical costs, quality of life and possibly survival.

Overall, the main limitations of the different approaches to measure the effect of HMEs used in pulmonary rehabilitation of laryngectomized patients are technical difficulties, the large inter- and intra-patient variability, the need to compare different patient groups, the small number of available patients, and possibly seasonal and national differences limit the statistical power of a study. The range of used methods, mentioned in Table 1, has made it possible to explore HME effects on different fields, but none of them is superior, they each have their advantages, disadvantages and limitations (summarized in Table 2). From a clinical point of view, (studies about) clinical effects of HME devices are providing the essential answers, however more fundamental research approaches should not be neglected because better understanding of HME function is needed for HME improvements.

**HME IMPROVEMENTS AND RESTORING THE PHYSIOLOGICAL HUMIDITY**

In chapter 4 we have found that more HME core material (weight) correlates with a higher humidity and a better water exchange performance. The limiting factor of HME performance is the amount of HME core material (where condensation and evaporation of water in the expired/inspired air take place). Adding more core material in an HME of the same size leads to a higher breathing resistance. Large HMEs are not feasible in laryngectomized patients for esthetical and practical reasons. So far, hygroscopic salt is the only option to increase humidity performance without increasing the amount of HME core material or HME size. The hygroscopic substance attracts an extra layer of water on the exchange surface
area of the core material in a wet environment (such as breathing). This extra water layer has a high heat capacity that contributes to the higher humidity performance (chapter 4). However, there is a limit to the amount of salt that can be added to the core material, because the amount of water might become so high that it might start dripping off the HME into the trachea or onto the clothes and airflow resistance of the HME might increase uncomfortably, because it gets clogged with water.

The ultimate purpose of an HME is to restore the humidity level in the trachea to the level, which existed before the surgery. We would then expect the patients to have optimal clinical benefit as the postlaryngectomy climate changes are the major cause of the clinical problems.\textsuperscript{41}

Chapter 4 has shown a wide range of HME performances among the different HME types tested, and the question is to what extent these HMEs are bridging the physiological humidity gap between nose and stoma breathing. The physiological tracheal climate during nose breathing is known for healthy volunteers and for surgically treated and radiated head and neck cancer patients with a temporary tracheotomy. As laryngectomized patients are also head and neck cancer patients having undergone surgery and radiation, the subglottic humidity value during nose breathing in this head and neck cancer patient group could be considered the ‘target humidity value’ in the upper trachea of laryngectomized patients\textsuperscript{29}, and not the humidity value in healthy volunteers.\textsuperscript{30}
Table 2. Advantages, disadvantages and limitations of different ways to assess HME effects.

<table>
<thead>
<tr>
<th>Measures</th>
<th>Methods</th>
<th>Pros</th>
<th>Cons</th>
<th>Limitations</th>
</tr>
</thead>
</table>
| Humidity and temperature | ACE In vivo | Direct measurement intra-tracheal climate changes contribution to understanding HME effect | - Technically difficult (condensation issues)  
- Requires a fast and heated humidity sensor.  
- Outcome dependent on placement of the probe intra-tracheal  
- Patient burden | - Not universally available and comparable |
| Humidity | Weighing method Ex vivo | - Less technically complicated than in vivo measurements  
- No patients required | - Requires a fast and heated humidity sensor | |
| Water exchange | Weighing method Ex vivo | - Technically easy and inexpensive  
- Universally applicable  
- Easy to understand for clinicians  
- No patients required | - Measure errors larger than humidity measurements | - Not for bibs, foam or extremely large/ deviating constructions |
| Water uptake | Weighing In vitro | - Easy and fast way to measure loss of hygroscopic substance | - Without effect/ performance of case and rest material  
- Indirect measure | - Only for hygroscopic HMEs |
| Water loss | ISO 9360-2:2001 In vitro | - International defined standard  
- No patients required | - Calibration pitfall  
- Complicated test setup  
- Time consuming | - Perhaps not entirely representative for in vivo situation |
## Measures

<table>
<thead>
<tr>
<th>Measures</th>
<th>Methods</th>
<th>Pros</th>
<th>Cons</th>
<th>Limitations</th>
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</thead>
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<tr>
<td>Lung function</td>
<td>In vivo</td>
<td>- Direct measurement</td>
<td>- No patients required</td>
<td>- Large intra-patient variability</td>
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<tr>
<td></td>
<td>Ex vivo</td>
<td>- Objective measure of mucus transport</td>
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<td>- Patient burden</td>
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<td></td>
<td>- Large intra-patient variability</td>
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<tr>
<td>Lung clearance</td>
<td>In vivo</td>
<td>- Objective measure of mucus transport</td>
<td></td>
<td>- Patient burden, not repeatable within 24-hours</td>
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<tr>
<td></td>
<td>Ex vivo</td>
<td>- Direct measurement</td>
<td></td>
<td>- Patient burden</td>
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<td>- Large intra-patient variability</td>
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<td></td>
<td>- Patient burden</td>
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<tr>
<td>Ciliated epithelium</td>
<td>In vivo</td>
<td>- Objective measure of mucus transport</td>
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<td>- Patient burden</td>
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<td></td>
<td>Ex vivo</td>
<td>- Direct measurement</td>
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<td>- Large intra-patient variability</td>
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<td>- Patient burden</td>
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<td></td>
<td>- Fractions seem not representative for secondary damage</td>
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<td>Clinical complaints</td>
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<td>- Not repeatable within 2-3 weeks</td>
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<td>Clinical outcome</td>
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<tr>
<td>Clinical infections</td>
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### Methods

- **Pressure drop/ISO 9360-2:2001**
  - Pros: Requires a sensitive pressure sensor, patient compliance and prescription by medical professionals, no patients required
  - Cons: Large intra-patient variability, large intra-patient variability, bias by instrumentation, large intra-patient variability, asymmetric intrapatient variability, patient burden
  - Limitations: Large intra-patient variability, patient burden, not repeatable within 24-hours

- **Spirometry**
  - Pros: In vivo measurement, objective measure of mucus transport
  - Cons: Large intra-patient variability, bias by instrumentation, patient burden
  - Limitations: Large intra-patient variability, not repeatable within 24-hours

- **Scintigraphy**
  - Pros: In vivo measurement, direct measurement
  - Cons: Technically complicated, bias by instrumentation, drift, patient burden
  - Limitations: Technically complicated, bias by instrumentation, drift, patient burden, not repeatable within 24-hours

- **Transcutaneous oxygenation monitor**
  - Pros: Ex vivo measurement, direct measurement
  - Cons: Technically complicated, drift, patient burden
  - Limitations: Technically complicated, drift, patient burden, not repeatable within 24-hours

- **Clinical complaints**
  - Pros: Clinical endpoints, clinical parameters, survey
  - Cons: No technical difficulties, easily comparable, clinical experts' opinions, combination of more parameters
  - Limitations: Clinical parameters, survey, retrospective collection, subjective
General discussion and future perspectives

Figure 1 shows the ex vivo humidity results of 23 HME types in solid red bars (chapter 4). All humidity values are normalized to an ambient humidity of 5 mg/L (black line in Figure 1). One can see that the best-performing HMEs increase the end inspiratory humidity clearly above ambient conditions (above 5 mg/L), and begin to approach the target value* for optimal physiological climate conditions in the trachea (nose breathing in head and neck patients with a temporary tracheotomy, blue striped bar*).

Figure 1. Overview of the ex vivo end-inspiratory humidity values of 23 HMEs (solid red bars) showing the gap with open stoma breathing (black line: 5mg/L) and nose breathing in head and neck patients (target value*, striped blue bar) with a temporarily tracheotomy. Preliminary results of alternatives for HME devices (bibs, scarf) are shown in the open bars. The horizontal line represents the ambient humidity (AH$_\text{amb_ref}$ of 5mg/L) that is used as reference value for all shown measurements.

Also shown in Figure 1 are some preliminary results of an ongoing (ex vivo) study of some traditional solutions for tracheostoma coverage, such as a bib (Buchanan, Kapitex, UK) or a scarf (open bars). Using a bib, scarf or even cotton baby bib, result in high end-inspiratory humidity values (Figure 1). This is not surprising as

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1 Measurements were performed using a heated plaster neck mall made of a laryngectomized patient with the heated humidity sensor and spirometer as previously described. Bibs and scarfs add some additional dead space between the device and the humidity sensor. In this case dead space (VD) cannot be neglected but with the relative magnitudes of equipment dead space of 100 ml and additional dead space of about 50 ml compared to the tidal volume (VT) of 500 ml these dead space effect are not substantial, as they will probably scale with (1 - VD/VT) (personal communication Klaus Zuckner).
bibs or other clothing (scarf) contain much more material (much larger in size) than HMEs and can therefore easily exchange more water/humidity than the small HME devices. However, there are some important practical disadvantages of using such options for stoma protection in rehabilitation. In case the perimeter of the bib is not connected to the skin and air leakage easily occurs (e.g. if the patient moves), the performance decreases immediately because the air will pass around the bib. In addition the bib will cause difficulties with airtight occlusion of the stoma, which is essential for speech. Moreover, the bibs become wet, which is uncomfortable for the patient, whereas the active part of an HME device is not in direct contact with the clothes and skin. An HME also prevents mucus spill on patient’s cloths/skin, and is easily changed after mucus coughing, whereas a bib is more difficult to keep clean from mucus spill. Such traditional ways of stoma covering could be helpful in poor countries, or extreme ambient conditions such as outdoors in winter and if used in addition to the HME.

In summary, using an HME improves instantaneously the humidification of the inspired air and is followed by decreased pulmonary complaints, improved tracheal ciliated epithelium and a decreased number of pulmonary infections. However, laryngectomized individuals still have impaired mucociliary clearance and are more susceptible for developing pulmonary infections compared to age-related individuals. There is still room for improvement of HMEs to close the gap to the most optimally ‘target’ humidity in laryngectomized patients in an acceptable size and will require an even better understanding of the function of an HME. Daily use of an HME is essential for comprehensive rehabilitation of laryngectomized patients.

SUGGESTIONS FOR FUTURE RESEARCH

The clinical effect of differences in performance of different HME types has not been assessed so far, although it seems logical that higher humidification capacity leads to better clinical results. For future research, it would be interesting to differentiate between humidity performances and the effect on ciliated cells and pulmonary complaints during several months. For example, a randomized study with a relatively high performing HME and a ‘dummy’ HME (e.g. the same HME but without salt) during 2 or 3 months in laryngectomized patients. Assessing pulmonary
complaints (or even pulmonary infections and corresponding treatment) and ciliary brush biopsies could help in understanding the relation between HME performance and clinical results. In the Netherlands it is difficult to start such a study in non-HME users due to very limited number of non-HME users as HME use is considered to be the standard of care in postlaryngectomy rehabilitation with a high compliance. It would therefore either have to be performed elsewhere or in HME users. In the latter case a first step should perhaps be to assess the relatively short-term effect of 24/48-hour removal of the HME in HME users.

Furthermore, HMEs have shown to increase the end-inspiratory humidity levels (chapter 2,3,4), but the temperature effects are not fully understood yet. As higher heat capacity performance leads to higher humidity exchange capacity, this is an interesting parameter to be studied in the future.

Another important parameter as topic for future research is the assessment of breathing resistance of HME devices and the resistance as experienced by patients. Chapter 4 gives information about the performance of HMEs regarding the humidity/water exchange aspect for many available HME types and can be used by medical professionals in prescribing HMEs to their patients. However, when a patient experiences an intolerable high resistance, next step for the medical professional should be to prescribe a different HME type with less resistance, but with still the most beneficial humidity capacity. This means that reliable resistance information must be available for all HMEs. The ISO 9360-2:2001 uses (completely) dry air instead of the ‘wet’ conditions during breathing, so there is no chance for building up an extra water layer on the surface of the HME core material. The additional extra water layer in hygroscopic HMEs will cause less space for (breathing) airflow to pass and it is possible that this increases the breathing air resistance. Indeed in Chapter 3 some patients have reported a higher resistance in the XM-HME compared the R-HME, which have a similar ISO pressure drop value. Also personal experience of breathing through different HME types (chapter 4) suggests large differences in airway resistance between HMEs with (almost) identical pressure drop values (ISO). The in vitro ISO pressure drop measurements seem therefore not completely representative for HME airway resistance performance in vivo. We believe that for clinical use, more detailed information about and insight in true HME breathing
resistance is essential to further improve medical care and pulmonary rehabilitation of laryngectomized patients.

New approaches to test the effects of HME use in patients could further be explored, such as measuring levels of nitric oxide and electron microscopy. Levels of nitric oxide have been used in studies on chronic lung disease patients such as asthma and COPD, and PCD.\textsuperscript{42,43} Laryngectomized patients have secondary chronic inflammation of tracheal epithelium as well, so it is conceivable that also in these patients increased levels of nitric oxide might be present, which theoretically could decrease after using an HME. Nitric monoxide could possibly function as a clinical indicator/marker for the status of chronic inflammation in TLE patients over months or even years. Electron microscopy has been used to study histological ultrastructural changes of airway epithelium\textsuperscript{44} and inflammatory cells in asthma. Electron microscopy has never been used in the evaluation of HMEs and also this could be a topic for future research.
REFERENCE LIST


General discussion and future perspectives


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