INFLUENCE OF HEAT AND MOISTURE EXCHANGER RESPIRATORY LOAD ON TRANSCUTANEOUS OXYGENATION IN LARYNGECTOMIZED INDIVIDUALS: A RANDOMIZED CROSSOVER STUDY

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Abstract: Background. High-resistance heat and moisture exchangers (HMEs) have been reported to increase transcutaneous oxygenation (tcpO2) values in laryngectomized individuals and to negatively influence patient compliance. The goal of the present study was to validate earlier published results on short-term transcutaneous oxygenation changes by high-resistance HMEs.

Methods. We conducted a randomized crossover study, monitoring the influence of an HME on tcpO2 over a 2-hour time interval in 20 subjects.

Results. No evidence of an immediate HME effect (95% CI: 14.9–13.3 mm Hg, p = .91), or a time-dependent HME effect (95% CI: -.121 – .172 mm Hg/minute, p = .74), on tcpO2 was found. After fitting the statistical model without time dependency, again no evidence of HME presence was seen (95% CI: -.5 mm Hg – 3.6 mm Hg, p = .15).

Conclusion. In contrast to earlier suggestions, there is no evidence of increased tcpO2 levels by high-resistance HMEs in laryngectomized individuals. Thus, using such HMEs has no added clinical value in this respect. ©2007 Wiley Periodicals, Inc. Head Neck 29: 1102–1110, 2007

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Total laryngectomy results in a permanent disconnection of the upper and lower airways, which leads to an increase of chronic pulmonary complaints like frequent involuntary coughing, excessive sputum production, and daily repeated forced expectoration in an attempt to clear the airway.
Heat and moisture exchangers (HMEs) were developed to compensate for the lost functions of the upper airway and have been found to lessen these symptoms and improve quality of life.\(^2-^5\)

After total laryngectomy, the upper airway is bypassed, so that total airway resistance is reduced as the laryngectomized individual breathes through the tracheostoma. Apart from preserving heat and moisture,\(^6\) HMEs substitute for this lost resistance of the upper airway to a certain extent. Depending on brand and flow, the resistance of commercially available HMEs ranges from less than 0.1 kPa s/L to values approximating the resistance of the upper airway, which is reported to be around 0.37 kPa s/L during nasal breathing at rest.\(^6-^8\)

The influence of an HME, and therefore of its resistance, on respiratory physiology has been evaluated in laryngectomized individuals by McRae et al.\(^9\) These authors reported that wearing an HME with a relatively high resistance of 0.32 kPa s/L for 4 hours increased the transcutaneous oxygenation (tcpO2) values with approximately 10.5 mm Hg (corresponding to an increase of approximately 20\% from baseline). It was assumed that the resistive load of the HME caused the collapsed lower airways to open, thereby improving the ventilation-perfusion ratio. Subsequently, it has been generally accepted that this phenomenon occurs,\(^3,^4,^8,^1^0-^1^2\) and currently a relatively high HME resistance is proposed to optimize pulmonary function in laryngectomy patients.\(^3,^9\)

Long-term patient compliance for HMEs is reported to be around 80\%.\(^1^3\) Suboptimal plaster adherence, skin irritation, and handling difficulties are some of the issues that affect patient compliance.\(^1^3\) Moreover, especially high-resistance HMEs can be experienced as unpleasant or even intolerable by the wearers, because they limit physical exertion too much, and compared with lower-resistance HMEs (of approximately 0.15 kPa s/L), compliance is limited.\(^3\) Furthermore, a closer read of the study by McRae et al reveals a limitation. No control group—in which 4-hour tcpO2 measurements were performed without an HME—was included. It is therefore not certain that the effect found by these authors can be attributed to the presence of a high-resistance HME. It was also not reported whether the tcpO2 values were obtained by discontinuous tcpO2 measurements or during continuous tcpO2 monitoring. Particularly if the tcpO2 values were obtained by continuous monitoring, the presence of the control group would be essential, since these types of transcutaneous measurements might be influenced by an on-patient upward signal drift of the tcpO2 electrode.\(^1^4\) On the other hand, discontinuous tcpO2 measurements at different locations introduce location dependency as an additional uncertainty, and when performed at the same location, the reaction of the skin on intermittent heated tcpO2 electrode is an unknown factor.

Because of the clinical consequences, and the fact that our current clinical belief is based on the results of 1 study, the goal of the present study was to reassess the influence of a high-resistance HME on transcutaneous oxygenation values in laryngectomized individuals.

**PATIENTS AND METHODS**

A randomized crossover study was conducted in 20 disease-free laryngectomized volunteers who were recruited from the outpatient clinic on the basis of availability. All participants were in long-term follow-up and at least 6 months posttreatment. The protocol was approved by the Protocol Review Board of the Institute, and written informed consent was obtained from all patients.

**Patient Characteristics.** The sample consisted of 19 men and 1 woman, and the median age was 64 years (range, 54–83 years). The median time since total laryngectomy was 7.0 years (range, 0.9–40.4 years). Eighteen patients received radiation therapy prior to or after the operation. Fourteen patients were consistent users of a Provox HME (Atos Medical AB, Hörby, Sweden): type “regular,” “high flow,” or incorporated in a hands-free speech valve. The resistance of these devices does not exceed 0.18 kPa s/L. One patient still smoked, and 1 patient had never smoked, and the median number of pack years of the total sample was 30.5 (range, 0–125 pack years). Two patients were aware of being diagnosed with chronic obstructive pulmonary disease (COPD). The median forced expiratory volume in 1 second (FEV1) (% predicted) was 75 (range, 52–103). Four patients used broncho-dilatory medication.

**The HME.** The HME used by McRae et al was reported to have a resistance of 0.32 kPa s/L.\(^9\) The HME used in our study was the Trachinaze, Kapitex Healthcare UK, incorporating the blue (night) filter unit, with a resistance of 0.37 kPa s/L (R. Falkenberg et al, personal communication). This resistance was measured according to the ISO9360 standard at an airflow of 30 L/minute,
the resistance of 0.32 kPa s/L, reported by McRae et al, was calculated at an intratracheal pressure of 0.150 kPa. Because McRae et al reported a close collaboration with Kapitek Heathcare, we assumed that the HMEs used in both studies were at least comparable, if not identical.

Although the pilot study showed no evidence of a time-dependent HME effect on tcpO2 (p = .61), see appendix, all volunteers were asked to remove their Provox HME from the tracheostoma, a period of at least 2 hours prior to visiting the hospital. This period was chosen for practical reasons, and to minimize any possible influence of the Provox HME on airway climate or respiratory physiology.

Transcutaneous Oxygenation Measurements.
The tcpO2 measurements were performed with a transcutaneous monitor (TINA TCM4, Radiometer Copenhagen, Denmark), connected to a combined transcutaneous pO2/pCO2 electrode (type E5280, Radiometer Copenhagen, Denmark). A new membrane was mounted on the electrode at least once a week, and the total tcpO2 data set for 1 patient was obtained with 1 membrane, in order to rule out possible changes in tcpO2 due to different membranes. After the electrode was covered with a new membrane, it was checked for 0 current. Prior to the first tcpO2 measurement of the day and after every change of measuring site, the transcutaneous electrode was calibrated with a 7.5% CO₂, 20.9% O₂, N₂ gas mixture, after which tcpO2 in ambient air was read out as an additional control parameter. All tcpO2 measuring sites were located on the peristernal region of the chest. Before placement of the plastic holder, in which the electrode was fitted, the skin was prepared according to the user manual’s instructions. In order to shorten the stabilization time on the skin, the smart heat option was used; ie, during the first 5 minutes after electrode placement, the electrode temperature was automatically raised to 45°C, after which it decreased to 44°C for the remaining measuring time on that site. The first tcpO2 value on a site was always obtained after a 15-minute stabilization time. A tcpO2 value was obtained by calculating the mean tcpO2 of a 5-minute time frame, to smooth noise. Since tcpO2 values obtained on the adult chest of hemodynamically stable patients are generally above 40 mm Hg, a tcpO2 value of <40 mm Hg obtained during the initial tcpO2 measurement on a peristernal site was considered “probably not representative” and a new site was prepared directly laterally to the original site. During the measurements, the subjects were seated in a comfortable chair in a semi-inclined upper body position. Furthermore, the subjects were asked not to communicate using tracheoesophageal speech, as this would cause the intra-airway pressure to rise substantially and influence the measurements.

Study Design. A major concern was the time-dependent impact of a heated electrode on the skin: tcpO2 readings during continuous tcpO2 monitoring have been described to be influenced by an upward transcutaneous electrode drift. To assess whether this phenomenon would bias the tcpO2 readings during continuous tcpO2 monitoring, it was decided to control for the tcpO2 readings obtained during continuous monitoring, by including a pair of discontinuous measurements, performed on a different peristernal site, 1 prior to and 1 after the continuous measurements. This pair of discontinuous measurements was performed on 1 single measuring site, since the pilot study in 6 patients (see appendix) indicated that intra-site tcpO2 variability was lower than intersite tcpO2 variability.

For each volunteer, the tcpO2 measurements were performed on 2 consecutive days: 1 day at sites C(ontinuous) and D(iscontinuous) and the other day at 2 other peristernal sites, CH and DH (where superscript “0” refers to the day of control measurement and superscript “H” refers to the day of HME measurement) (Figure 1). To eliminate a sequence effect, the day of HME installment was randomly chosen. To rule out diurnal variation in lung function, the measurements started at the same time on both days. The moment the patient had been installed in the chair was referred to as t = 0 (Figure 2).

The discontinuous tcpO2 measurements were performed on sites D⁰ and D⁷. A baseline tcpO2 was performed as soon as possible after t = 0, after which the electrode was removed from its plastic skin holder, and replaced again, after the continuous measurements, in order to obtain the second tcpO2 value. As a result, the second tcpO2 value was obtained 130 minutes after baseline measurement, corresponding to 100 minutes after HME placement (further referred to as long-term discontinuous measurements). In the 30-minute time interval before HME placement, the electrode was prepared and used for obtaining the baseline tcpO2 value for the continuous measurement (Figure 2).
The continuous tcpO2 measurements were performed on site C0 and CH. In between the continuous tcpO2 measurements, the transcutaneous electrode remained on the skin. After having obtained a baseline tcpO2 at C0/H, a tcpO2 value was obtained 15 minutes (further referred to as short-term continuous measurement) and 70 minutes later, respectively (further referred to as long-term continuous measurement). The HME was installed directly after the baseline measurement at CH. After the last continuous measurement the electrode was prepared and used for the second discontinuous measurement, and consequently this tcpO2 value was obtained 30 minutes later (Figure 2).

Room temperature and humidity were obtained using a temperature and humidity sensor (TESTO BV Almere, The Netherlands). The room temperature and humidity values, obtained daily just prior to the start of the tcpO2 measurements, were used for further analysis. The tcpO2 output of the TCM4 monitor, the room temperature and the humidity traces were simultaneously recorded on a PC (via a multichannel data acquisition system and Chart 5.4.1 software, ADinstruments).

**Statistical Analysis.** Analyses were based on a mixed-effect analysis of (co)variance with tcpO2 as dependent variable. Based on the results of the pilot study (see appendix), it was calculated that 20 subjects were sufficient to demonstrate a tcpO2 increase of 5 mm Hg due to the presence of an HME, with a power of 80% using a 2-sided significance level of \( p < .05 \). The baseline model included fixed effects of site, day, presence of HME, time since \( t = 0 \), time on site of electrode since first tcpO2 measurement at that specific site (=time of continuous monitoring), time since placement of HME (set at 0 on the day without HME, first measurement at D1 and first measurement at C1), FEV1, room temperature and relative humidity. Random effects (ie, between patients, between days or between site differences in tcpO2) were included for overall mean, day (between patients), time since start (between patients and between days within patients), site (between patients and days), time since electrode placement (between patients, days, and sites), absence/presence of HME (between patients, days, and sites) and time since HME placement (between patients, days, and sites). However, to simplify the random effects model, a backward elimination procedure (all variables are included to start with; variables with the highest \( p \)-value \( > .05 \) are then removed stepwise from the model) was used on the random effects, based on the restricted maximum-likelihood (REML) based Akaike’s Information Criterion. Calculations were performed using the function lme of the statistical package S+ version 6.2.

**RESULTS**

A complete dataset was obtained for all 20 subjects. The discontinuous tcpO2 measurements on sites D0 and D1 were performed at median times \( t0 + 22–27 \) minutes, and \( t0 + 2 \) hours 33–38 minutes. During continuous monitoring on sites C0 and CH the tcpO2 values were obtained at median times \( t0 + 52–57 \) minutes, \( t0 + 1 \) hour 07–12 minutes, and \( t0 + 2 \) hour 02–07 minutes. The HME was installed on CH at median time \( t0 + 57 \) minutes. Inspection of the data suggested the presence of 1 outlier, as was confirmed by the subsequent analysis of covariance. The means and standard deviations of the changes in tcpO2 during the various time intervals are shown in...
Table 1. The net HME effect is unlikely to exceed 5 mm Hg. Furthermore, in both control and HME groups, during long-term continuous monitoring the tcpO2 readings seem to increase while in the discontinuous measurements in both groups a slight decrease is observed.

**Mixed Effect Analysis of Covariance.** The backward elimination procedure resulted in elimination of the random effects “time since HME placement,” “HME presence,” “Day,” and “Time since start (between days within patients).” Elimination of any other random effect resulted in a decrease of the REML-based AIC. Residual analysis based on the model identified the presence of 1 outlier (“Patient 7”, short-term measurement at $C^H$, see also Figure 3). This value was excluded from further analysis. No other major violations of the model (non-normality, heteroscedasticity, non-linearity) were detected.

There was no evidence of an immediate effect of presence of the HME pO2 after placement (95% CI of intercept: $-14.9 - 13.3$ mm Hg, $p = .91$). Neither was there evidence of a (linear) time-dependent effect on tcpO2 due to the presence of the

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<th>Table 1. Mean transcutaneous oxygenation changes, mm Hg (standard deviation) during the various time intervals.</th>
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<td><strong>Control measurements</strong></td>
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HME (95% CI of slope: -.121 – .172 mm Hg/minute, p = .74). Figure 4 shows the mean tcpO2 values estimated from the statistical model.

When the statistical model was fit without a time since HME effect on tcpO2, again no evidence of presence of an HME is seen (95% CI: -.5 mm Hg–3.6 mm Hg, p = .15). During continuous monitoring, ie, after the 15 minutes electrode stabilization period, the tcpO2 still increased, in the latter model on average by .081 mm Hg/minute (SE .016, p < .0001) in both control and HME measurements. In contrast, in relation to t = 0, there was also an indication of a downward trend in the tcpO2 values (if obtained by noncontinuous monitoring) throughout the whole measuring period with an average of .029 mm Hg/minute (SE .010, p = .0070). No systematic effects were found for pulmonary function: FEV1 (% predicted), room temperature (median, 23.8°C; range, 20.6°C–25.0°C), or relative humidity (median, 38.6%; range, 26% to 57%).

DISCUSSION

In this study, no evidence of an effect of the presence of an HME on tcpO2 was found in a group of volunteers with an age distribution that we think is representative for the laryngectomee population.5 The findings of the present study are in contrast with the findings of McRae et al, who observed a mean tcpO2 increase of approximately 10.5 mm Hg (p = .0087) in 25 subjects after 4 hours of HME use.9 Although it is unknown whether these authors have obtained the tcpO2 values by discontinuous measurements or during continuous monitoring, it seems likely that the latter method was used, as their results are in complete agreement with the tcpO2 changes observed during continuous monitoring in the present study. Our results also showed that the presence of a control group is essential in order to correctly interpret the results of the HME measurements, because the increase in tcpO2 readings during the continuous monitoring and the overall decrease in tcpO2 values were present in both the HME and the control measurements. Because no control group was included in the study of McRae et al, the tcpO2 changes observed by these authors might not represent an HME effect. If these authors have indeed obtained the tcpO2 values during continuous monitoring, it is probable that the reported tcpO2 increase is at least biased by an upward signal drift of the transcutaneous electrode.14

In contrast to our study, with a maximal time frame 100 minutes after HME placement, McRae et al evaluated tcpO2 values 4 hours after placement of the device. However, it is highly unlikely that a 4-hour follow-up in the present randomized study would have shown evidence of an effect of the presence of an HME on tcpO2: the pilot study, which was also carried out with a 4-hour tcpO2 follow-up after HME placement (see appendix), as well as the present randomized study showed no evidence of a time-dependent HME effect on tcpO2.

During the last decades, several hypotheses have been postulated with regard to the consequences of changes in upper airway resistance in laryngectomized individuals. Some authors assume that the loss of upper airway resistance increases dynamic airway compression by shifting the equal pressure point toward a more peripheral airway region, where the airway has less elasticity and is more easily flattened.18 Others suggest that the respiratory load of the HME creates positive end-expiratory pressure (PEEP), thereby reducing alveolar collapse and improving lung volumes.9 However, these theories have not been validated in laryngectomized individuals. In addi-
tion, in the general literature on lung function, more complicated mechanisms have been forwarded by respiratory physiologists. It should be noted that PEEP is probably not a viable theory because an HME only establishes additional positive pressure during expiration; at the very end of expiration, the endotracheal pressure must be atmospheric, because there is an open connection between the airway and the environment.

However, there is circumstantial evidence in favor of a possibly relevant effect of HME resistance on respiratory physiology. Pursed lips breathing (PLB), like the HME, increases extrathoracic expiratory breathing resistance by creating additional expiratory load and has been shown to improve arterial oxygenation values in patients with COPD. Notably, according to some authors, this is the consequence of a decreased breathing rate, rather than a direct consequence of the increased airway resistance. Since the additional expiratory load of a high resistance HME approaches that of PLB, a selective subgroup of laryngectomees, ie, those who suffer from severe COPD, may also have respiratory benefits from the resistive load of this device. Since no subjects with severe obstructive disease were identified in this study, no comment can be made on the validity of this hypothesis. Furthermore, it should be noted that, in contrast to PLB, an HME also increases inspiratory resistance. This may not be tolerated for a longer period of time, particularly by those with severe COPD. To validate the above-mentioned hypothesis, the ideal HME—in analogy to PLB—should increase breathing resistance mainly during expiration, which has also been suggested earlier.

Apart from evaluation of a short-term HME effect on tcpO2, the research group of McRae et al also assessed the long-term influence of the HME on tcpO2 in a randomized control trial. It was found that in contrast to the control group, tcpO2 was increased after wearing an HME for 6 months. It was suggested by the authors that this increase was also directly related to the increased extrathoracic resistance due to the HME. However, it should be noted that this can also be hypothesized to be the result of a generally improved mucosa condition, concurrent with the

FIGURE 4. The mean transcutaneous oxygenation (tcpO2) values estimated from the statistical model. The dotted line represents the heat and moisture exchanger measurements and the solid line the control measurements. The standard errors are indicated at the various points in time.
improvement of pulmonary symptoms (the authors found a significant decrease in infection rate, coughing, mucus production, and shortness of breath during rest in the HME group), due to chronically increased intra-airway temperature and humidity values created by the HME.

The golden standard to measure HME influences on blood oxygenation would be with the aid of arterial blood gasses. This eliminates the influence of the skin and electrode drifts, which limit the accuracy of the present study. However, the arterial puncture itself may cause physical distress, eg, an altered heart rate and breathing pattern, which may influence the results as well, and therefore placement of an arterial catheter would be required. Because of its invasive character, arterial blood gas sampling was not considered justified in this stage of research. Nevertheless, additional research with the aid of arterial blood gas sampling may be required to validate the discussed hypotheses and/or to confirm the results of the present study.

It has to be stressed that our findings do not dispute the positive clinical effects of HMEs on respiratory symptoms and quality of life, which have been demonstrated by several clinical studies. However, the present study does indicate that high HME resistance is probably not as beneficial as was thought previously. Furthermore, because high HME resistance may negatively influence patient compliance, we advocate the use of HMEs with a convenient resistance.

CONCLUSION
We conclude that, in contrast to earlier suggestions, there is no evidence of increased tcpO2 levels due to the presence of a high-resistance HME in laryngectomized individuals. Since high-resistance HMEs have been found to negatively influence user comfort and thus compliance, HMEs with a convenient breathing resistance can be the first choice.

APPENDIX: THE PILOT STUDY
A pilot study was performed in 6 laryngectomized subjects. The materials, methods, and statistical approach of this pilot study were identical to those of the subsequent randomized trial, except that in the pilot study (a) none of the volunteers were users of an HME, (b) the day of HME installment was not randomly assigned, (c) the influence of the HME on the tcpO2 values was observed for a time interval, comparable to that of the study of McRae et al: 2 hours of continuous monitoring at sites C and CH, and a 4-hour tcpO2 evaluation point by discontinuous measurements at sites D and DH, and (d) just prior to the 4-hour evaluation, the tcpO2 value was also obtained on 2 other measuring sites in the peristernal region of the chest to assess between-site variability. The statistical analysis of the pilot study showed no evidence of a systematic effect of presence of HME (p = .74). Also there was no evidence of a time-dependent HME effect on tcpO2 (p = .61). Furthermore, it was found that during continuous tcpO2 monitoring, in spite of a 15-minute stabilization period, the measured tcpO2 at a specific site still increased on average by .13 mm Hg/mimute (SE .02; p < .0001), both in control and HME measurements. The maximal systematic difference in tcpO2 between 2 sites was 16.1 mm Hg, with additional random variation of 6.7 mm Hg. Variability between measurements on 1 site was 2.4 mm Hg.

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REFERENCES
8. Verkerke GJ, Geertsema AA, Schutte HK. Airflow resistance of airflow-regulating devices described by independ-


