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

van den Boer, Cindy

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Chapter 3

Ex vivo water exchange performance and short-term clinical feasibility assessment of newly developed heat and moisture exchangers for pulmonary rehabilitation after total laryngectomy

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Cindy van den Boer
Sara H. Muller
Andrew D. Vincent
Klaus Züchner
Michiel W.M. van den Brekel
Frans J.M. Hilgers
ABSTRACT

Background: Laryngectomized patients suffer from respiratory complaints due to insufficient warming and humidification of inspired air in the upper respiratory tract. Improvement of pulmonary humidification with significant reduction of pulmonary complaints is achieved by the application of a heat and moisture exchanger (HME) over the tracheostoma. The aim of this study was to determine whether the new Provox HMEs (XM-HME and XF-HME) have a better water exchange performance than their predecessors (R-HME and L-HME respectively; Atos Medical, Hörby, Sweden). The other aim was to assess the short-term clinical feasibility of these HMEs.

Methods: The XM-HME and XF-HME were weighed at the end of inspiration and at the end of expiration at different breathing volumes produced by a healthy volunteer. The associations between weight changes, breathing volume and absolute humidity were determined using both linear and non-linear mixed effects models. Study-specific questionnaires and tally-sheets were used in the clinical feasibility study.

Results: The weight change of the XM-HME is 3.6 mg, this is significantly higher than that of the R-HME (2.0 mg). The weight change of the XF-HME (2.0 mg) was not significantly higher than that of the L-HME (1.8 mg). The absolute humidity values of both XM- and XF-HME were significantly higher than that of their predecessors. The clinical feasibility study did not reveal any practical problems over the course of three weeks.

Conclusions: The XM-HME has a significantly better water exchange performance than its predecessor (R-HME). Both newly designed HMEs did succeed in the clinical feasibility study.
INTRODUCTION

The respiratory system plays an important role in the defense of the internal environment through the rapid optimization or conditioning of the humidity and the temperature of the inspired air. The optimal humidity, i.e. 100% saturation, is achieved by the evaporation of water from the respiratory epithelium. The optimal body temperature (37°C) is achieved by turbulent and convective heating. The region in the respiratory tract where the optimal humidity and temperature levels of the inspired air are reached is called the isothermal saturation boundary (ISB). In healthy individuals, the ISB is reached within short distance (25 cm) from the nostrils to a few centimeters below the carina. After a total laryngectomy (TL), the upper airway tract, i.e. the first 16 cm, is bypassed by the permanent tracheostoma, corresponding with the former subglottic level. Consequently, the ISB level is shifted downwards, and a longer segment of the tracheobronchial epithelium is exposed to relatively cold and dry air. It is not surprising, therefore, that laryngectomized patients develop respiratory problems and pulmonary symptoms, such as frequent involuntary coughing, repeated forced expectoration for airway clearance, and recurrent pulmonary infections.

Improvement of the reduced air-conditioning after total laryngectomy can be achieved by the application of a heat and moisture exchanger (HME) covering the tracheostoma. An HME is a passive heater and humidifier that restores part of the upper airway climate conditioning. In randomized clinical trials, the use of an HME has been proven to be effective in the reduction of pulmonary complaints and to significantly improve the quality of life after a total laryngectomy.

Currently, a wide variety of types and brands of HMEs are commercially available, and for medical professionals, it is not always readily clear as to what HME would be optimal for which patient. Therefore, objective and clinically relevant data concerning the performance of the various HMEs is required.

For the assessment of HME performance until recently, two methods were available: the in vitro water loss lung model as defined by the ISO standard committee and in vivo intra-tracheal humidity and temperature measurements in laryngectomized patients. Both these approaches, however, require complex and technically challenging instrumentation, and the results of the various tests are not always
readily comparable. Recently, we have developed a novel and simplified ex vivo method for HME performance assessment. This method enables a straightforward assessment of the water exchange performance of an HME by measuring the weight changes of the HME over the breathing cycle. The weight difference between the end of expiration (maximum HME weight because of the highest water content) and the end of inspiration (minimum HME weight because of the lowest water content) is a measure for the water retention capacity of the HME. The ex vivo method is used to measure HME performance in this study.

In a recent study by Scheenstra et al, it was demonstrated that two newly developed prototype HMEs (Rplus-HME and Lplus-HME) with improved ISO 9360-2:2001 water loss values showed a significantly better end-inspiratory humidity ($AH_{\text{insp}}$) in vivo compared to their predecessors (R-HME and L-HME, respectively). Subsequently, van den Boer et al could confirm this outcome with the ex vivo water exchange performance method and with comparable $AH_{\text{insp}}$ values. The clinical feasibility study of these prototype HMEs, however, indicated some technical shortcomings with respect to the occlusion system for tracheoesophageal voicing. Therefore, two new successor Provox HMEs (XtraMoist-HME (XM) and XtraFlow-HME (XF)) were developed to optimize the closing mechanism for voicing while retaining improved HME performance. The primary aims of the present study were to determine whether the water exchange performance of these new HMEs, as assessed with the ex vivo HME-weighing method, is better than that of their predecessors (the R-HME and L-HME, respectively) and to also assess the short-term feasibility and clinical experience of patients with these new HMEs. A secondary aim of this study was to further validate the ex vivo HME weighing method by the simultaneous registration of $AH_{\text{insp}}$.

**MATERIAL AND METHODS**

**HME devices**

Two newly developed, commercially available HME devices, manufactured by Atos Medical, Sweden have been tested in this study: the Provox XtraMoist HME (further called XM-HME), and its lower airflow resistance version, the Provox XtraFlow HME (further called the XF-HME). Both HMEs were compared to their predecessors,
respectively the R-HME (short for the Provox Normal HME) and its lower airflow resistance version the L-HME (short for the Provox HiFlow HME) and to the prototypes Rplus-HME and Lplus-HME. All of these devices consist of a plastic case with a volume of 5 ml filled with hygroscopic foam impregnated with calcium chloride. An overview of the HME manufacturer specifications for the commercially available HMEs is given in Table 1. In clinical use, devices are placed over the stoma, fixed in a separate peristomal adhesive or an intra-tracheal cannula. All HMEs need to be replaced at least every 24 hour to prevent bacterial overgrowth. Airtight closure for speech is obtained by pressing the top of the cap with a finger.

The most relevant technical change in the newly developed HMEs is that the volume of the foam material considerably has been increased by filling the space for the spring mechanism of the R- and L-HME and using the recoil capacity of the foam as a spring for the occlusion mechanism. Moreover, small adjustments have been made in diameter, configuration, and color of the top lid (larger), to ameliorate voicing (Figure 1).

Table 1. In vitro HME specifications (according to ISO standard 9360-2:2001) as provided by the manufacturer (Atos Medical, Hörby, Sweden)

<table>
<thead>
<tr>
<th>HME type</th>
<th>Water loss (mgH2O/L)</th>
<th>Pressure drop (Pa)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>at tidal volume of 1 liter</td>
<td>at 30 L/min</td>
</tr>
<tr>
<td>L-HME</td>
<td>24.4</td>
<td>66</td>
</tr>
<tr>
<td>R-HME</td>
<td>23.7</td>
<td>89</td>
</tr>
<tr>
<td>XF-HME</td>
<td>24.0</td>
<td>40</td>
</tr>
<tr>
<td>XM-HME</td>
<td>21.5</td>
<td>70</td>
</tr>
</tbody>
</table>
Study design and measurement configuration

The XM-HME and XF-HME are measured in the same test configuration (shown in Figure 2) and following the same protocol as for the previously measured R-HME, L-HME, Rplus-HME and Lplus-HME. In short, a healthy volunteer breathes through the HME device that is placed on a test configuration including a spirometer (Flowhead MLT300 ADInstruments GmbH Oxfordshire, UK), and a heated capacitive hygrometer with a response time of 0.1 - 0.2 s. HME breathing is performed until the water saturation equilibrium of the HME is reached. From this time point on, 25 repeated breathing episodes are performed, alternately ending at inspiration.
or expiration, using variable breathing patterns (tidal, shallow and deep breathing) recorded with the spirometer. After each breathing episode, the HME is weighed on a microbalance (Sartorius MC210P, Göttingen, Germany). The differences between the weight at end-expiration (maximum) and end-inspiration (minimum) of consecutive breathing episodes are obtained. This results in 21 weight changes, as the first weight change at the start of the registration and the weight changes between the different breathing patterns are discarded. Accuracy and repeatability for weight measurements were within 0.1 mg. For analysis the end-inspiratory absolute humidity was used ($AH_{\text{insp}}$). The HMEs are tested with a healthy volunteer (first author) under room climate conditions. Environmental humidity and temperature were monitored with a commercial, calibrated humidity sensor (Testo BV, Almere, The Netherlands). The dead space in the test set-up is approximately equal for all measurements, approaching 100 ml. Absolute humidity values were registered and saved with Acquis 2.8 software and were exported to Microsoft Excel. The spirometer and humidity sensor are calibrated as described previously.$^{15,17}$ Spirometer data were registered with Powerlab software (ADInstruments GmbH Oxfordshire, UK).

**Figure 2.** Test configuration. The healthy volunteer breaths through the spirometer (left side), which is connected to a T-shaped tube containing an absolute humidity sensor. At the end of this T-tube, the HME is connected (right).
Data normalization

Data normalization on weight and humidity measurements was applied to correct for the environmental differences in humidity between measurements, as described earlier. For all measurements, data were converted to a reference ambient absolute humidity (\(AH_{\text{amb-ref}}\)) of 5 mg/L.

Statistical methods

The data of the XM-HME and XF-HME are added to the previously published data for analysis (L-HME, R-HME, Lplus-HME and Rplus-HME). The assessment of associations between weight change and average breathing volume and between end-inspiratory absolute humidity and inspiratory breathing volume are previously described in van den Boer et al. In short (for more details see appendix 1), for each HME type, the association between weight change and average breathing volume was determined using a linear mixed effects model, and the association between end-inspiratory absolute humidity and inspiratory breathing volume was determined using an exponential-decay, nonlinear least-squares regression. The level of significance is set at 0.05. Using inverse variance weighted correlation, weight changes of the HME types were compared both at a breathing volume of 0.5 L, corresponding with the average tidal volume in laryngectomized patients and at a breathing volume 1.0 L, corresponding to the standard ISO water loss conditions.

Short-term feasibility study

Short-term feasibility and practical aspects of the XM-HME and XF-HME were investigated in a prospective clinical study using convenience sampling for patient inclusion. The primary aim of this observational study was to be informed about patient’s short-term comfort and clinical experience with the new HME devices.

Twenty laryngectomized patients, 18 males and 2 females, (mean age 66 years; range 51 – 82 years), were included. All patients were previously treated with radiotherapy (12 pre- and 8 postoperative), had quit smoking, were regular HME users, and were in long-term follow-up (median 11 years, range 2-23 years postlaryngectomy). Twelve patients used the R-HME day and night, and five
patients combined the R-HME with the L-HME (with lower breathing resistance) during physical activities or at night. One of these patients used the R-HME at night and the Provox Freehands HME (automatic speech valve) during daytime. Three patients exclusively used the L-HME.

R-HME users received the XM-HME and L-HME users received the XF-HME and were instructed to use them during 3 weeks. At the end of the test period, a study-specific questionnaire was obtained and a tally sheet was used to report the daily frequency of coughing and mucus expectoration during the first 3 days of the first week and during the last 3 days of the third week. The protocol of the feasibility study was approved by the Protocol Review Board of the Institute and written informed consent was obtained from all patients.

RESULTS

The 21 weight changes of XF-HME, XM-HME and their predecessors (L-HME and R-HME, respectively) as a function of the average breathing volume are shown in Figure 3. The plotted lines are the estimates of the statistical model and connect the different breathing patterns (tidal, shallow and deep breathing). As can be seen, the XM-HME clearly shows a higher weight change than the XF-, R- and L-HME.

The end-inspiratory absolute humidity values as a function of the end-inspiratory breathing volume are shown in Figure 4. As can be seen, the humidity values vary between HME types, but all are higher than the humidity levels obtained in breathing through the test configuration without HME attached. Again the XM-HME yields the highest values.

Table 2 presents the model estimates of the weight changes at breathing volumes of 0.5 and 1.0 L and $AH_{\text{insp}}$ values at a breathing volume 0.5 L of all six HME types (see the dashed vertical lines in Figure 3 and 4). The differences between the new HMEs (XF-HME and XM-HME) have been tested for significance compared to the R-HME and L-HME and to their corresponding prototype HMEs (Rplus / Lplus). The XM-HME has a significant higher weight change and higher $AH_{\text{insp}}$ value compared to both the L-HME and R-HME. The Rplus-HME has a significant higher weight change and $AH_{\text{insp}}$ value compared to the XM-HME.
Figure 3. Weight change (mg) as a function of the average breathing volume (L) per HME type. Dashed vertical lines indicate the breathing volumes of 0.5 and 1.0 L used for comparison of the HMEs (Table 2). The reference ambient absolute humidity ($AH_{amb-ref}$) was chosen at 5 mg/L. The L-HME and R-HME data were previously published, the Lplus- and Rplus-HME can also be found in but are not shown in this Figure for visual clarity. The parameters describing the plotted statistical model estimates are given in Table 4 of Appendix 1.
Figure 4. End-inspiratory absolute humidity (mg/L) as function of the end-inspiratory breathing volume (L) at AH\textsubscript{amb-ref} of 5 mg/L. HME performance was compared at a breathing volume of 0.5 liters (the dashed vertical line). The L-HME and R-HME data are as previously published, the Lplus- and Rplus-HME data can also be found in [15] but are not shown in this Figure for visual clarity. The parameters describing the plotted statistical model estimates are given in Table 5 of Appendix 1.
Table 2. Overview of HME performance. The estimated values (standard errors) of the $AH_{\text{insp}}$ and weight change at breathing volume of 0.5 and 1.0 L (normalized to $AH_{\text{amb-ref}} = 5\text{mg/L}$) and the tested differences between HME types. P-value (***) are given for pairwise comparisons and data published in van den Boer et al\textsuperscript{15} are marked with an asterisk (*).

<table>
<thead>
<tr>
<th>Variable</th>
<th>$AH_{\text{insp}}$ (mg/L) at 0.5 L</th>
<th>Weight change (mg) at 0.5 L</th>
<th>Weight change (mg) at 1.0 L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without HME*</td>
<td>5.33* (0.10)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L-HME*</td>
<td>7.25* (0.11)</td>
<td>1.84* (0.15)</td>
<td>3.64* (0.19)</td>
</tr>
<tr>
<td>R-HME*</td>
<td>8.46* (0.11)</td>
<td>2.00* (0.10)</td>
<td>3.56* (0.11)</td>
</tr>
<tr>
<td>XF-HME</td>
<td>8.44 (0.15)</td>
<td>1.95 (0.15)</td>
<td>3.64 (0.18)</td>
</tr>
<tr>
<td>versus L-HME</td>
<td>1.19 (0.19)***</td>
<td>0.11 (0.20)</td>
<td>0.00 (0.25)</td>
</tr>
<tr>
<td>versus R-HME</td>
<td>0.02 (0.19)</td>
<td>0.05 (0.17)</td>
<td>0.08 (0.20)</td>
</tr>
<tr>
<td>versus Lplus-HME</td>
<td>-0.92 (0.24)***</td>
<td>-0.36 (0.20)</td>
<td>-0.02 (0.24)</td>
</tr>
<tr>
<td>XM-HME</td>
<td>10.83 (0.15)</td>
<td>3.63 (0.15)</td>
<td>6.14 (0.18)</td>
</tr>
<tr>
<td>versus L-HME</td>
<td>3.58 (0.26)***</td>
<td>1.79 (0.20)***</td>
<td>2.50 (0.25)***</td>
</tr>
<tr>
<td>versus R-HME</td>
<td>2.37 (0.26)***</td>
<td>1.63 (0.17)***</td>
<td>2.58 (0.20)***</td>
</tr>
<tr>
<td>versus Rplus-HME</td>
<td>-2.04 (0.36)***</td>
<td>-0.65 (0.20)***</td>
<td>-1.38 (0.26)***</td>
</tr>
</tbody>
</table>

* Published in Van den Boer et al\textsuperscript{15}

**p-value < 0.05

The correlation between the weight change results and the water loss values (ISO standards 9360-2:2001) as reported by the manufacturer (see also Table 1;\textsuperscript{15}) for the six HMEs is shown in Figure 5. The relation between the weight change and $AH_{\text{insp}}$ measurements of these six HME types is shown in Figure 6.
Figure 5. Relation between weight changes and ISO water loss values for breathing volume of 1.0 L and at AH_{amb-ref} of 0 mg/L (ISO standards conditions). The ISO values are transformed to negative values for optimal visualization. The inverse variance weighted $R^2$ is 0.79. The vertical bars represent the standard errors, which are not available for the ISO water loss values.

Figure 6. Comparison of six HMEs using the weight change during the breathing cycle. Values are normalized to AH_{amb-ref} of 5mg/L at a breathing volume of 0.5 L. The inverse variance weighted $R^2$ is 0.96. The vertical and horizontal bars represent the standard errors.
**Clinical feasibility study**

Twenty patients were in this study, one patient was excluded from further analysis due to suffering a cold during the test period. Completed questionnaires were available for 19 patients and tally sheets were available for 17 patients. Eighteen patients used the new devices day and night during the total study period of 21 days. One patient used the new HME devices only during daytime.

**1. Mucus and Coughing**

Table 3 presents the outcome of the questionnaires and tally sheets concerning reports on mucus production and coughing frequency. On average between 47% and 53% of the patients reported a decrease in mucus production and a decrease between 37%-41% in coughing frequency. None of the patients reported an increase in mucus production or coughing frequency.

**Table 3. Results of the study specific questionnaires and tally sheets of decrease in mucus production and coughing frequency**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Questionnaire available (n)</th>
<th>Mucus decrease</th>
<th>Coughing decrease</th>
<th>Tally sheets available (n)</th>
<th>Mucus decrease</th>
<th>Coughing decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>XM-HME</td>
<td>10</td>
<td>40 %</td>
<td>30 %</td>
<td>9</td>
<td>44 %</td>
<td>44 %</td>
</tr>
<tr>
<td>XF-HME</td>
<td>5</td>
<td>40 %</td>
<td>40 %</td>
<td>5</td>
<td>60 %</td>
<td>40 %</td>
</tr>
<tr>
<td>Both</td>
<td>4</td>
<td>75 %</td>
<td>50 %</td>
<td>3</td>
<td>67 %</td>
<td>33 %</td>
</tr>
<tr>
<td>Total</td>
<td>19</td>
<td>47 %</td>
<td>37 %</td>
<td>17</td>
<td>53 %</td>
<td>41 %</td>
</tr>
</tbody>
</table>

**2. Breathing resistance**

Two patients using both the XM- and XF-HME switched to full-time XF-HME use after approximately 10 days due to the uncomfortable breathing resistance with the XM version. Of the remaining XM-HME users, four patients also reported an increase in breathing resistance, while four patients experienced easier breathing and six patients did not report any difference compared to the R-HME. Of the XF-HME group, one patient reported difficulty breathing. Compared to the L-HME, three patients experienced more breathing resistance with the XF-HME and two experienced no difference in this respect.
3. Speech

None of the patients reported any valve sound while closing the XM- and XF-HMEs for sound production. The speaking valve was reported to function comparable to the accustomed HMEs in 13 patients, while 4 patients reported easier airtight closure. One patient experienced a better voice during the test period with XM-HME, and one patient had more difficulties speaking long sentences and more difficulties with airtight valve occlusion compared with the regular HME. Overall, 12 patients preferred the new HME devices, three preferred their predecessor HME devices whereas four patients expressed no preference.

DISCUSSION

This study shows that, based on the ex vivo weight change and humidity assessments, the XM-HME and the XF-HME indeed perform better than their predecessors R-HME and L-HME, respectively. In the case of the XM-HME, both the water exchange capacity and $AH_{insp}$ values exceed those of the R-HME. The XF-HME exhibited significantly better $AH_{insp}$ values than the L-HME, but not a significant difference for the weight change. This latter observation may be due to the somewhat smaller discriminative power of the ex vivo weight change method compared to that of the in vivo humidity measurements, as also discussed in the recent validation study of the ex vivo method. The better performance of the XM- and (partly) the XF-HME compared to their predecessors is primarily due to the larger volume of foam impregnated with calcium chloride able to retain more water, which results in a higher water capacity and therefore a higher water exchange (weight change) value.

The secondary aim of this study was the additional validation of the ex vivo method weighing method. The weighing method directly measures the amount of water deposited in the HME during one breathing cycle of a volunteer. The ISO standard measures the cumulative water loss of an artificial lung breathing at a tidal volume of 1 L during 24 hours. Figure 5 shows the correlation between the ex vivo weight changes (at 1 L) and the in vitro ISO water loss values of the tested HMEs. The inverse variance weighted $R^2$ between the weight change and ISO water loss is 0.79, which is in line with the previously published Figure of only four HMEs (the L-HME, R-HME, and the prototype Lplus-HME and Rplus-HME) with a correlation of 0.77.
6 shows the relationship between the ex vivo water exchange (weight change) at the clinical relevant tidal volume of 0.5 L and the resulting end-inspiratory absolute humidity just behind the HME ($R^2$ is 0.96). This $AH_{\text{insp}}$ is the equivalent of the $AH_{\text{insp}}$ measured in vivo in patients. Also this Figure shows that the weighing method is a valid measure of HME performance.

The $AH_{\text{insp}}$ and weight changes of both the previously tested prototype Rplus-HME and the new XM-HME are significantly better than the other HMEs, but the Rplus-HME was even significantly better than the XM-HME. However, the top lid of the prototype Rplus-HME functioned suboptimal, because it produced a disturbing noise while closing it for voicing, as already mentioned in the introduction. Therefore, optimization of the speaking valve was imperative, and as can be concluded from the results of the clinical feasibility study, this was achieved. The XM-HME appears to have a sufficient airtight occlusion system for speech as reported by the patients in the clinical feasibility study. Moreover, after a short period, almost half of all patients reported decreased mucus production and lower coughing frequency. The clinical feasibility study also revealed that the majority of patients prefer the XM-HME and the XF-HMEs, which are clinically relevant from a compliance point of view. Therefore it is conceivable that the manufacturer decided to produce the XM- and XF-HME, but these results also show that there is potential for further improvement of water exchange performance.

The clinical feasibility study, however, also produced some puzzling results concerning the perceived breathing resistance of the new devices. Some patients reported easier breathing with the XM-HME compared to the R-HME, while others reported the reverse. Two patients, who were accustomed to use a combination of the R-HME and the L-HME, were unable to combine the XM- and the XF-HME due to the uncomfortable breathing resistance of the XM-HME. An explanation for this phenomenon could be that the XM-HME contains more water at the surface of the foam pores in the HME, which in some patients might result in a perceived increased breathing resistance. According to the in vitro pressure drop values (ISO 9360-2:2001), as provided by the manufacturer (Table 1), the pressure drop of the XM-HME is not much higher than that of the R-HME. However, ISO standard pressure drop measurements are performed under dry environmental circumstances and these values obviously do not correspond to the patients’ internal and external
environmental conditions.\textsuperscript{9,19} These observations underscore that breathing resistance always will have to be taken into account in the development of HMEs, when attempts are made to further improve water exchange performance.

A major advantage of the ex vivo HME-weighing method is that it is not necessary to perform these measurements in laryngectomized patients. Previous data on the values obtained with five additional volunteers have shown that one volunteer is enough for valid measurements.\textsuperscript{15} Hence the results in the present study most likely will be similar when the assessment is carried out with a laryngectomized patient-volunteer. This opens the possibility to carry out a comparative assessment of more HME types and brands with the ex vivo test method, something that is planned for future studies.

CONCLUSION

The XM-HME shows a significantly better water exchange performance than its commercially available predecessor, the R-HME. In the case of the XF-HME, the water exchange performance is slightly, but not significantly better than that of its predecessor, the L-HME. The results of this study, in combination with the earlier published HME data, also form an additional validation of the ex vivo water exchange weighing method. Since both the XM-HME and the XF-HME successfully passed the clinical feasibility test, this new generation HMEs can replace their predecessors as the standard HMEs for pulmonary rehabilitation of laryngectomized patients in clinical practice.

ACKNOWLEDGEMENTS

This study (in part) was funded through an unrestricted research grant of Atos Medical AB, Hörby, Sweden.
APPENDIX 1

Parameters of Figures 3 and 4.

Table 4. Parameters of the fit of Figure 3, weight versus average breathing volume using all inspiration data and expiration data during tidal breathing (as the estimate of initial value).

Equation 1: \( \text{Weight change} = \beta^H_0 + \beta^H_M + \beta^H_1 \times \log(\text{Volume}) + \varepsilon_i \)

where
1. \( \beta^H_0 \) and \( \beta^H_1 \) are the fixed-effect intercepts and slopes for the HME types.
2. \( \beta^M \sim N(0, \sigma^M_2) \) are the random intercepts per measurement period.
3. \( \varepsilon_i \sim N(0, \sigma^R_2) \) are the residuals.

<table>
<thead>
<tr>
<th>HME</th>
<th>( \beta^H_1 )</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-HME</td>
<td>2.56</td>
<td>0.31</td>
</tr>
<tr>
<td>L-HME</td>
<td>2.24</td>
<td>0.19</td>
</tr>
<tr>
<td>XF-HME</td>
<td>2.44</td>
<td>0.30</td>
</tr>
<tr>
<td>XM-HME</td>
<td>3.63</td>
<td>0.27</td>
</tr>
</tbody>
</table>

SE = standard errors of the estimated slopes.

Table 5. Exponential decay model of \( AH_{\text{insp}} \) versus inspiratory breathing volume (Figure 4), during tidal breathing (as the estimate of initial value).

Equation 2: \( AH = \beta^H_0 + (\beta^H_{AS} - \beta^H_0) \times \exp[-\exp(\beta^H_{DR} \times \text{Insp Vol})] + \varepsilon_i \)

where
1. \( \beta^H_0 \), \( \beta^H_{AS} \) and \( \beta^H_{DR} \) are the intercept, asymptote and the log of the decay rate for each HME.
2. \( \varepsilon_i \sim N(0, \sigma^R_2) \) are the residuals.

<table>
<thead>
<tr>
<th>HME</th>
<th>( \beta^H_{AS} )</th>
<th>( \beta^H_0 )</th>
<th>( \beta^H_{DR} )</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Est</td>
<td>SE</td>
<td>Est</td>
</tr>
<tr>
<td>Without</td>
<td>5.12</td>
<td>0.05</td>
<td>31.67</td>
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<td>L-HME</td>
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</tr>
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<td>R-HME</td>
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<tr>
<td>XM-HME</td>
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<td>0.34</td>
<td>33.33</td>
</tr>
</tbody>
</table>

Est = estimated value; SE = standard error of estimate.
REFERENCE LIST


