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Under-humidification and over-humidification during moderate induced hypothermia with usual devices

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Abstract *Objective:* In mechanically ventilated patients with induced hypothermia, the efficacy of heat and moisture exchangers and heated humidifiers to adequately humidify the airway is poorly known. The aim of the study was to assess the efficacy of different humidification devices during moderate hypothermia. *Design:* Prospective, cross-over randomized study. *Settings:* Medical Intensive Care Unit in a University Hospital. *Patients and participants:* Nine adult patients hospitalized after cardiac arrest in whom moderate hypothermia was induced (33°C for 24 h). *Interventions:* Patients were ventilated at admission (period designated "normothermia") with a heat and moisture exchanger, and were randomly ventilated during hypothermia with a heat and moisture exchanger, a heated humidifier, and an active heat and moisture exchanger. *Measurements and results:* Core temperature, inspired and expired gas absolute and relative humidity were measured. Each system demonstrated limitations in its ability to humidify gases in the specific situation of hypothermia. Performances of heat and moisture exchangers were closely correlated to core temperature ($r^2 = 0.84$). During hypothermia, heat and moisture exchangers led to major under-humidification, with absolute humidity below 25 mgH_2O/l. The active heat and moisture exchanger slightly improved humidification. Heated humidifiers were mostly adequate but led to over-humidification in some patients, with inspiratory absolute humidity higher than maximal water content at 33°C with a positive balance between inspiratory and expiratory water content. *Conclusions:* These results suggest that in the case of moderate hypothermia, heat and moisture exchangers should be used cautiously and that heated humidifiers may lead to over-humidification with the currently recommended settings.

Keywords Adverse effects · Heated humidifiers · Heat and moisture exchangers · Humidification devices · Hypothermia · Mechanical ventilation

Introduction

Use of moderate induced hypothermia at 33 °C is a neuroprotective strategy after cardiac arrest, which has shown reduction of mortality and of neurological sequelae in two recent randomized controlled trials [1, 2]. A consensus has now emerged and recommends 12–24 h of mild hypothermia in this indication [1, 2, 3, 4]. Although this issue is still debated [5, 6, 7], some authors advocate the use of mild hypothermia during brain injury with elevated intracranial pressure [8, 9, 10]. Hypothermia has been evaluated in this indication for prolonged periods, up to 14 days [8]. In a recent meta-analysis, McIntyre showed that beneficial effects of hypothermia after traumatic brain injury were more marked in the case of prolonged hypothermia (> 48 h) [5]. Recently, Jiang et al. showed that 5 days of mild hypothermia, in comparison with 2 days, led to a better outcome and improved intracranial hypertension control in patients with severe traumatic brain injury [11].

Hypothermia may also show a protective effect in different disorders and is tested in experimental conditions such as hemorrhagic or endotoxic shock [12, 13, 14]. This suggests potential for a larger use of this technique. Despite the fact that hypothermia is usually performed in invasively ventilated patients, the systems used for gas humidification and warming during mechanical ventilation are never detailed, and this aspect has not been studied. Hypothermia, however, is a source of several theoretical problems with the most frequently used humidification devices, and inadequate humidification over a prolonged duration may induce deleterious clinical consequences such as bronchial injury and atelectasis [15].

Heating and humidification of gas may be achieved with any of three main devices, heat and moisture exchangers (HME), heated humidifiers (HH), and more recently with active HME. The working principle of HME is based on the condensation of expiratory water content and subsequent delivery of water to the patient during the next inspiration [16]. In case of hypothermia, the water content of the expiratory gas is decreased, potentially leading to a lower efficiency of HME (Fig. S1), and these devices are frequently contraindicated when core temperature is lower than 32 °C [17, 18]. Such recommendations, however, are not based on clinical hygrometric measurements, and no evaluation has been performed with the most recent generations of hygroscopic and hydrophobic HME. HH devices are based upon evaporation of water in the humidification chamber, depending on the heater plate temperature [19]. During hypothermia, HH could theoretically lead to over-humidification. Indeed, the maximum water content of a gas is 36 mg H_2O/l at 33 °C, while HH can deliver up to 44 mg H_2O/l in stable conditions with the currently recommended settings (40 °C at chamber, 37 °C at Y-piece) [20] (Fig. S1). No specific setting exists for HH in the specific situation of hypothermia.

Because recommendations for profound hypothermia are based on the working principles of older generations of heat and moisture exchangers and have not been confirmed by hygrometric measurements [21], we performed this study to compare the humidification performances of the different humidification devices during moderate induced hypothermia after cardiac arrest.

Material and methods

The study was conducted in the intensive care unit of Henri Mondor Hospital. Patients admitted from June 2, 2003, to December 15, 2003, for cardiac arrest with indication of neuroprotective hypothermia were prospectively included after information of the family. The ethics committee of the Société de Réanimation de Langue Française, approved the study and waived the requirement for signed consent. No patient was supposed to have a core temperature lower than 32 °C, and thus all systems could be used without limitations.

The protocol used to induce hypothermia was the one recently described [1]. Patients were covered with a wet sheet, and ice was placed on lower limb vascular axes. Continuous analgesia-sedation by fentanyl and midazolam was associated and with a continuous infusion of paralyzing agent to avoid shivering. The target core temperature was between 32 °C and 34 °C. This temperature had to be obtained in less than 4 h, maintained for 24 h, followed by passive rewarming obtained by stopping use of wet sheet, paralyzing agents, and ultimately sedation.

Tested humidification devices

Three different systems were tested:

1. A standard hydrophobic and hygroscopic heat and moisture exchanger (HME) (Hygrobac, Tyco Healthcare, Plaisir, France)
2. An “active” heat and moisture exchanger (Humid-Heat, Hudson, Dardilly, France). To use this device, an estimated level of minute ventilation must be set (with a maximum of 30 l/min), influencing the quantity of added water. In this study, we used two settings of estimated minute ventilation: 15 l/min (noted aHME 15) and 30 l/min (aHME 30).
3. A standard heated humidifier (HH) (MR 850, Fisher & Paykel, Villebon, France), with a standard temperature of 37 °C at the humidification chamber and of 40 °C at the *Y* piece. This setting is supposed to deliver a gas–water content of approximately 36.5 mg H_2O/l to the patient [19, 22].

HME was used initially while the patient was still in normothermia; then, all devices were randomly evaluated during the period of hypothermia. A total of four periods after normothermia were performed in random order: HME, active HME successively set 15 l/min or 30 l/min, and HH. Each device was left in place during a mean of 6 h. Measurements were performed after a minimum of 3 h to reach a steady state.

Measured parameters

Core temperature and hygrometric measurements were obtained in all conditions. Patients’ temperatures were measured with a calibrated tympanic thermometer (Genius, Sherwood Medical, Crawly, UK), and ambient air temperature was measured with a high precision thermometer (Duotemp, Fisher & Paykel, Auckland, New

Zealand). Hygrometric measurements of both inspired and expired gases were performed with the noninvasive psychrometric method, as previously described [23]. During normothermia, inspired hygrometry was not measured in two patients and expiratory humidity was not measured in two patients. Expired humidity was not measured in four patients with the HH during hypothermia.

Statistical analysis

Levels of hygrometry in the five different periods were compared with nonparametric tests. An analysis of variance was first performed with a Friedman test, followed by paired analysis by Wilcoxon test. Correlation coefficients have been obtained by simple regression analysis. *P* values smaller than 0.05 were considered significant. Values are expressed in median (25th–75th interquartile ranges), unless otherwise specified.

Results

Twelve patients met the inclusion criteria, but three patients with hemodynamic instability could not be enrolled in the study. Main characteristics of the nine included patients are shown in Table 1. The median ambient air temperature during the study periods was 24.0 °C (minimum 20 °C; maximum 26.5 °C) without any significant difference among the study periods.

Core temperature

The initial core temperature of the patients before induced hypothermia was 37.2 °C (36.1–37.5 °C) (period called normothermia), with a minimum of 35.5 °C and a maximum of 37.9 °C. During hypothermia, the median core temperature was 32.8 °C (31.9–33.2 °C), without any statistically significant difference among the devices. Core temperature during the different periods is shown in Fig. 1.

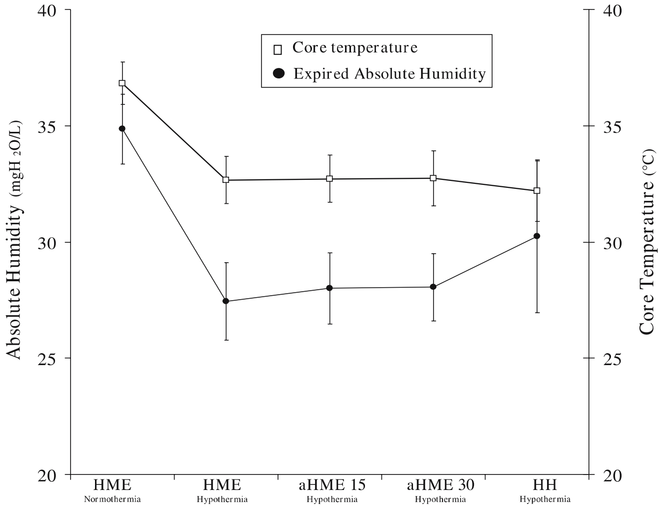

Fig. 1 Absolute humidity (mg H_2O/l) of the expired gases and core temperature (°C) during the different study periods. The hygrometry of expired gas (mean ± SD) is represented by *bold dots*, and core temperature is represented with *squares*. Hygrometry of expired gas was significantly reduced during hypothermia in comparison with normothermia periods. Mean values are displayed with standard deviation. (*aHME 15* active heat and moisture exchanger set at 15 l/min, *aHME 30* active heat and moisture exchanger set at 30 l/min, *HH* heated humidifier, *HME* heat and moisture exchanger)

Hygrometric measurements

Individual and mean values of inspiratory and expiratory absolute humidity (expressed in mg H_2O/l) for expired and

Table 1 Main characteristics of included patients (*CA* cardiac arrest, *ICU LOS* length of ICU stay, *IH* in hospital, *NA* not available, *OH* out of hospital, *SAPS II* simplified acute physiology score)

	Age (years)	SAPS II	ICU LOS (days)	Time before resuscitation (minutes)	Duration of the resuscitation (minutes)	Location of the CA	Etiology of the CA
Patient 1	23	81	6	NA	20	OH	Drug overdose
Patient 2	72	112	5	NA	NA	OH	Unknown cause
Patient 3	57	92	2	NA	NA	OH	Unknown cause
Patient 4	45	51	3	30	15	OH	Hypoxemia (aspiration)
Patient 5	49	93	3	1	20	OH	Hypoxemia (asthma)
Patient 6	76	101	3	15	20	OH	Hypoxemia (aspiration)
Patient 7	67	77	15	1	20	OH	Hypoxemia (terminal respiratory insufficiency)
Patient 8	73	105	6	1	15	IH	Hypoxemia (cardiogenic pulmonary edema)
Patient 9	37	62	5	20	3	OH	Ventricular fibrillation
Mean	55	86	5.3	11.3	16.1		
SD	18	20	3.9	12.3	6.3		

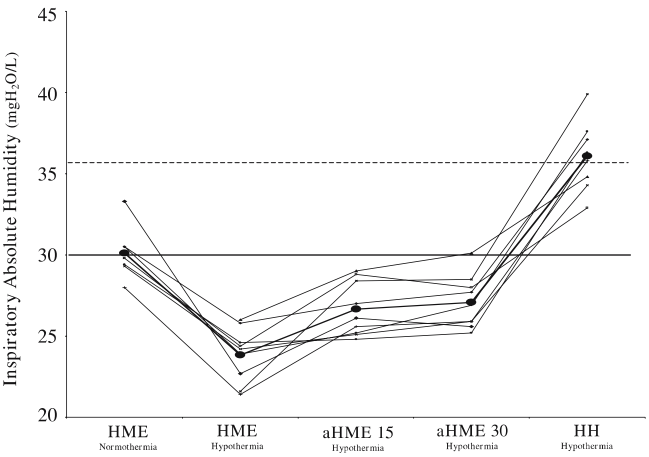

Fig. 2 Absolute humidity (mg H_2O/l) of the inspired gases during the different study periods. Individual and mean (*bold dots* and *thick line*) values are represented. The *dotted horizontal line* corresponds to the maximal water content of a gas at 33 °C (36 mg H_2O/l). The *horizontal thick line* corresponds to the minimum hygrometry of gas recommended for invasive mechanical ventilation. Very low levels of hygrometry were measured during hypothermia with HME; with HH, hygrometry of inspired gas was above the maximal water content at 33 °C in half of the patients, leading to condensation inside the airways (*aHME 15* active heat and moisture exchanger set at 15 l/min, *aHME 30* active heat and moisture exchanger set at 30 l/min, *HH* heated humidifier, *HME* heat and moisture exchanger)

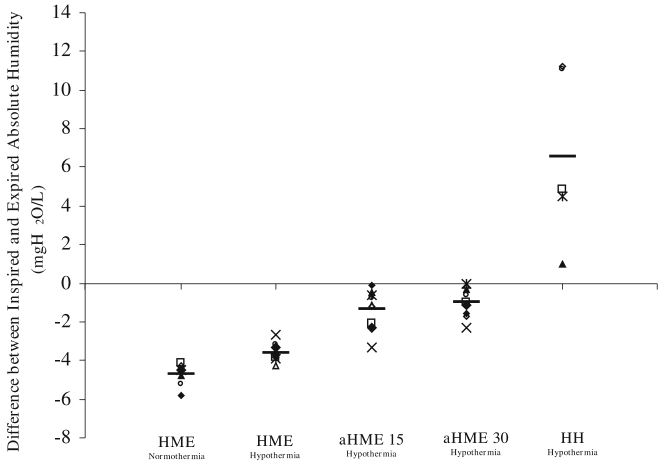

Fig. 3 Difference between inspired and expired absolute humidity in mg H_2O/l with the tested devices. With HME, the difference between inspired and expired absolute humidity was negative; with HH, the balance was positive an average of 6 mg H_2O/l for each respiratory cycle. Individual values are represented by *different symbols*; mean is represented by *straight lines* (*aHME 15* active heat and moisture exchanger set at 15 l/min, *aHME 30* active heat and moisture exchanger set at 30 l/min, *HH* heated humidifier, *HME* heat and moisture exchanger)

inspired gases during the different periods are shown in Figs. 1 and 2.

During normothermia with the heat and moisture exchanger, hygrometry of the inspired gas was 29.8 mg H_2O/l (29.4–30.5). During hypothermia, hygrometry of the inspired gas was significantly different among the studied devices: the lowest values were observed with the heat and moisture exchanger (24.2 mg H_2O/l, 22.7–24.6 mg H_2O/l) reaching a minimum of 21.4 mg H_2O/l. Intermediate values were obtained with active heat and moisture exchanger at both tested settings (26.1 mg H_2O/l, 25.2–28.4 mg H_2O/l), and the highest values were obtained with the heated humidifier, with 36.1 mg H_2O/l (34.7–37.2 mg H_2O/l), $p < 0.0001$. The levels of humidification delivered by heat and moisture exchangers were higher during normothermia than hypothermia ($p = 0.01$).

Hygrometry of the expired gas was also significantly higher during normothermia than hypothermia 34.6 mg H_2O/l (34.2–35.3) vs. 27.7 mg H_2O/l (26.4–28.2) ($p < 0.01$), but there was no significant difference for expiratory hygrometry among the devices during hypothermia ($p = 0.14$), possibly due to the small sample size for the heated humidifier period. Relative humidity of the expired gases remained constant during hypothermia above 95% (Fig. S2). The same is true for inspired gases except for active heat and moisture periods (Fig. S3).

Differences between inspired and expired humidity

The differences between inspired and expired humidity are shown in Fig. 3.

Absolute humidity was lower in the inspired than in the expired gas with heat and moisture exchangers and with active heat and moisture exchangers. With heat and moisture exchanger, the difference between inspired and expired absolute humidity was on average minus 4.1 ± 0.8 mg H_2O/l and was similar in normothermia and hypothermia. The heat and moisture exchangers thus delivered to the patient a mean of 87% of the expired water content. With active heat and moisture exchangers, the difference between inspired and expired absolute humidity was only mildly negative. On the contrary, the absolute humidity was higher in the inspired than in the expired gas with heated humidifiers (plus 6.1 mgH_2O/l).

Relationship between core temperature and inspired and expired hygrometry

With heat and moisture exchangers, a strong correlation was found between absolute humidity of expired gases and core temperature (Fig. 4). A strong correlation was also found between hygrometry of inspired gas and core temperature (Fig. 4). In addition, a strong correlation existed between hygrometry of inspired and expired gas in the case of heat and moisture exchangers, in line with the working principles of these devices (Fig. 5).

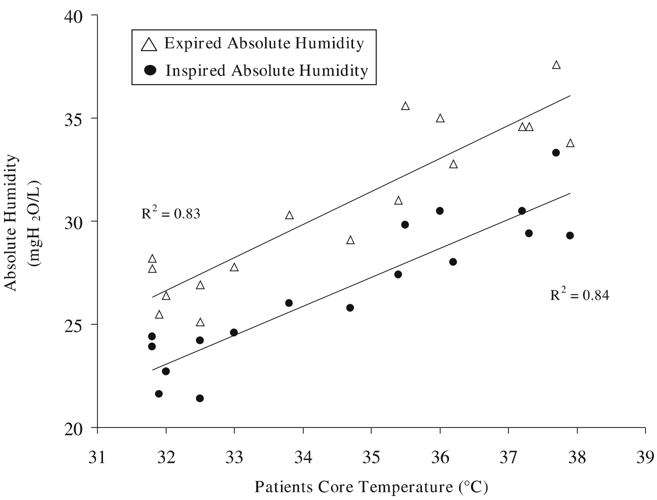

Fig. 4 Correlation between both expired and inspired gas hygrometry and core temperature with heat and moisture exchangers. A good correlation was found between expired gas hygrometry (represented by *triangles*) and core temperature, according to the relationship between a gas temperature and its maximal water content at saturation (see additional data). Hygrometric HME performances (i.e., inspired gas hygrometry), represented by *bold dots*, strongly correlated with the core temperature. During moderate hypothermia (32–34 °C), performance was very low (*HME* heat and moisture exchanger)

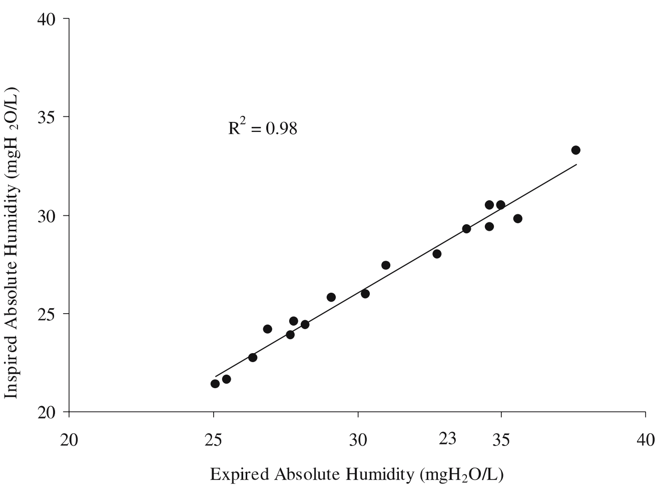

Fig. 5 Correlation between inspired and expired absolute humidity of the gas (expressed in mg H_2O/l) with heat and moisture exchangers (*HME*). A strong correlation was found between inspired and expired gas hygrometry with heat and moisture exchangers. With these high performing HME, the rate of inspired humidity corresponded to 87% of expired humidity

Discussion

The influence of moderate hypothermia on the hygrometric performances of the different humidification devices was assessed in the present study. A great influence of the core temperature was present with heat and moisture exchangers. Hypothermia was associated with a marked reduction of hygrometric performances (water content delivered to patients) of the heat and moisture exchangers, explained by a reduction of expired absolute humidity during hypothermia (Figs. 1 and 2). Performances of the heated humidifier were not reduced by hypothermia, but could lead to excessive humidification in some cases.

One reason to perform this study has been the clinical observation of several cases of atelectasis in patients treated with hypothermia in our unit. In this study, we found that the main humidification devices do not work ideally in the specific situation of hypothermia. Clinical impact of under-humidification with heat and moisture exchangers and of possible over-humidification with heated humidifiers was, however, not assessed in this study. Occurrence of bronchial lesions, atelectasis and endotracheal tube occlusion have clearly been described in the case of under-humidification [24–26]. The risk of atelectasis has also been suggested in the case of over humidification [27], although never demonstrated during clinical studies. Suctioning needs may also be increased in case of over-humidification, with associated risks of hemorrhage and de-recruitment [28]. Moreover, during the period of hypothermia, minute ventilation needs to be reduced to avoid metabolic alkalosis owing to the decrease of metabolism and carbon dioxide production [29], The reduction of the tidal volume should be even more pronounced if a heated humidifier is used, considering the reduced dead space [30]. These last effects may further increase the risk of atelectasis. The clinical consequences of an inadequate humidification (under- or over-humidification) should be even more pronounced if induced hypothermia is prolonged, as suggested for brain trauma [5, 8]. Over shorter durations of hypothermia, as indicated for neuroprotection after cardiac arrest, clinical consequences of a non-optimal humidification may also exist. Indeed, several animal [15] and human [31] studies showed that bronchial lesions (inflammation, epithelial cell injury, mucociliary clearance impairment) may be present after only several hours of mechanical ventilation with poorly humidified gas. Associated with immunosuppression induced by hypothermia [32], the occurrence of bronchial lesions and of atelectasis could lead to an increased risk of nosocomial pneumonia in these patients [33].

There are no clear recommendations concerning the optimal level of humidification during hypothermia. The hygrometric results obtained with heat and moisture exchangers are consistent with the hypothesis of a strong influence of the core temperature on this device performance. There is no measurement of the performances of the heat and moisture exchangers during hypothermia in the literature to compare with our results. Recommendations to avoid these devices in case of hypothermia are based on theoretical principles, and it is recommended not to use heat and moisture exchangers when core temperature is lower than 32 °C [17]. In the present study, very low levels of hygrometry were obtained with heat and moisture exchangers during moderate hypothermia, reaching the levels associated with endotracheal tube occlusion [24, 25, 34]. The minimal level of humidity recommended during prolonged mechanical ventilation is 30 mg H_2O/l [18]. Endotracheal tube occlusion is a rare complication with most recent heat and moisture exchangers [35–40]. However, bronchial lesions, atelectasis and partial endotracheal occlusion usually associated with under-humidification may occur for normal values [15, 41]. In the present study, heat and moisture exchanger performances were very low during hypothermia, although the tested devices were among the most efficient currently [21]. It is likely, even if not assessed in this study, that less efficient heat and moisture exchangers would perform even worse during hypothermia. The clinical consequences of low levels of humidification during short durations of hypothermia may be limited in comparison with prolonged durations of induced hypothermia [8, 11].

In the present study, inspired relative humidity remained stable with heat and moisture exchangers during hypothermia, in contrast to inspired absolute humidity (Figs. 2, S3). It has been suggested in a bench study that relative humidity may be more important than absolute humidity [42]. The impact of relative in comparison with absolute humidity is, however, barely documented.

This study shows for the first time the relationship between hypothermia and the water content of the expired gas, with an inverse relationship between the core temperature and the expired absolute humidity (Fig. 4). This was one hypothesis of this study, based on the physical principles of thermodynamics. A strong correlation between expired-gas and inspired-gas absolute humidity was found for heat and moisture exchangers, consistent with the working principles of these devices (Fig. 5) [16].

In the present study, the performances of heated humidifiers were not influenced by hypothermia. The levels of absolute humidity of inspired gas during hypothermia are comparable to those published in patients with normothermia [19] or on a bench test using the psychrometric method [43] or other methods [22]. The lack of impact of core temperature on heated humidifier performances is consistent with its working principles [20], and this humidification device was able to provide an acceptable level of absolute humidity, higher than 30 mg H_2O/l. The results of the study, however, also showed the possibility of over-humidification with these systems during hypothermia when using the currently recommended settings, with unclear clinical consequences. Indeed, the difference between inspired and expired absolute humidity was always positive: the inspired water content was on average 36.1 mg H_2O/l, while the expiratory water content was 30.2 mg H_2O/l, leading to a positive balance of 6.1 mg H_2O/l (this balance being of –4.1 mg H_2O/l with heat and moisture exchangers). Another cause of over-humidification exists in this situation: the inspired water content was at 36.1 mg H_2O/l, with values up to 39.9 mg H_2O/l, while the maximal water content of a gas at 33 °C is only 36 mg H_2O/l. Water condensation occurs in the respiratory system when the water content exceeds the maximal water content at a given temperature (Fig. S1). Clinical consequences of this over-humidification are not well known [27]. However, animal studies have suggested a possible impact on respiratory mechanics related to altered surfactant activity [44], to alterations of gas exchanges and decrease in lung compliance, possibly due to distal micro-atelectasis and alveolar collapse [45].

A common idea is that the use of heated humidifiers makes difficult the induction of hypothermia; however, this has been poorly documented. This study was not designed to assess this aspect accurately. Nevertheless, it should be noted that the same level of hypothermia could be achieved with the heated humidifier and with the filters, for 6 h. The possibility of preventing hypothermia induction if a heated humidifier is used during a 24-h period is not known, but laws of physics suggest that this influence should be limited.

Specific heated humidifiers' settings should be developed to achieve humidification above the recommended level of 30 mg H_2O/l and lower than the maximal water content of 36 mg H_2O/l at 33 °C, in order to avoid excessive delivery of free water to the lower airway.

Active heat and moisture exchangers showed intermediate results. As with standard heat and moisture exchangers, lower expiratory water content leads to a reduction of their performances, as encountered in patients with hypothermia. The extra-added water, however, is not dependent on the presence of hypothermia. No major difference was found in the performance of this device between the settings of 15 l/min and 30 l/min (Fig. 2). We previously measured their performances during normothermia, in a bench study, with values of inspired hygrometry around 33–35 mg H_2O/l in conditions simulating normothermia [46]. In the present study, during hypothermia, levels of humidification remained lower than recommended, but never below 25 mg H_2O/l, as observed with standard heat and moisture exchangers (Fig. 2). This may be insufficient in the case of prolonged periods of hypothermia. The balance between inspiratory and expiratory absolute humidity was close to zero with this humidification device (Fig. 3). The relative humidity of the inspired gases was significantly lower with these active heat and moisture exchangers in comparison with heated humidifiers and passive heat and moisture exchangers. This may be explained by the working principles of the active HME, as the device is heated, reducing the relative humidity. This may suggest insufficient external water addition with this system.

In conclusion, this study has shown that, during induced hypothermia, both under-humidification and over-humidification exist with typical humidification devices. Use of heat and moisture exchangers leads to a marked under-humidification with well known associated risks. These devices should be used cautiously and only for short periods in the case of moderate hypothermia. Use of heated humidifiers during hypothermia with currently recommended settings carries the potential risk of over-humidification, with possible deleterious effects on respiratory mechanics (micro-atelectasis, decrease in lung compliance and surfactant impairment), in addition to other problems related to these devices [19, 43, 47]. Aside from deleterious effects of hypothermia, clinicians must be aware of the well known risks of atelectasis, bronchial lesions and endotracheal tube occlusion in the case of heat and moisture exchanger use, particularly in the case of prolonged hypothermia. The potential clinical deleterious effects with the different humidification devices raised by this study have not been demonstrated, and clinical studies specifically designed for this purpose are required. These results confirm that humidification devices do not provide stable humidification and are influenced by patient temperature as well as external conditions [19, 48]. These conditions should be considered to optimize the choice of the device used.

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