Title page

Title:

Use of Normothermic Default Humidifier Settings Causes Excessive Humidification of Respiratory Gases during Therapeutic Hypothermia

Running Head:

Humidity of respiratory gases during cooling

Authors:

Shoichiro Tanaka, MD.

Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Division of Neonatology, St Mary's Hospital, Fukuoka, Japan.

Sachiko Iwata, MD, PhD.

Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Masahiro Kinoshita, MD.

Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Kennosuke Tsuda, MD, PhD.

Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Sayaka Sakai, MD.

Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Mamoru Saikusa, MD.

Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Ryouta Shindou, MD.

Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Eimei Harada, MD, PhD
Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Junichiro Okada, MD, PhD.
Division of Neonatology, St Mary's Hospital, Fukuoka, Japan.

Tadashi Hisano, MD.
Division of Neonatology, St Mary's Hospital, Fukuoka, Japan.

Hiroshi Kanda, MD.
Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Yasuki Maeno, MD, PhD.
Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Yukiko Araki, PhD.
Biostatistics Centre, Kurume University School of Medicine, Fukuoka, Japan.

Kazuo Ushijima, MD, PhD.
Department of Anaesthesiology, Kurume University School of Medicine, Fukuoka, Japan.

Teruo Sakamoto, MD, PhD.
Advanced Emergency Medical Service Centre, Kurume University Hospital, Fukuoka, Japan.

Yushiro Yamashita, MD, PhD
Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Osuke Iwata, MD, PhD.
Department of Paediatrics and Child Health, Centre for Developmental and Cognitive Neuroscience, Kurume University School of Medicine, Fukuoka, Japan.

Address for correspondence:
Dr Osuke Iwata

Centre for Developmental and Cognitive Neuroscience
Department of Paediatrics and Child Health, Kurume University School of Medicine
67 Asahimachi, Kurume, Fukuoka 830-0011, Japan
E-mail: o.iwata@ucl.ac.uk
Tel: +81-942-31-7565 Fax: +81-942-38-1792

Abstract

Background:

Adult patients frequently suffer from serious respiratory complications during therapeutic hypothermia. During therapeutic hypothermia, respiratory gases are humidified close to saturated vapour at 37˚C (44mg/L) despite that saturated vapour reduces considerably depending on the temperature reduction. Condensation may cause serious adverse events, such as bronchial oedema, mucosal dysfunction and ventilator-associated pneumonia during cooling.

Methods: To determine clinical variables associated with inadequate humidification of respiratory gases during cooling, humidity of inspiratory gases was measured in 42 cumulative newborn infants who underwent therapeutic hypothermia. Three humidifier settings of 37-default (chamber-outlet, 37˚C; distal circuit, 40˚C), 33.5-theoretical (chamber-outlet, 33.5˚C; distal circuit, 36.5˚C), and 33.5-adjusted (optimised setting to achieve 36.6mg/L using feedback from a hygrometer) were tested to identify independent variables of excessively high humidity >40.6mg/L and low humidity <32.9 mg/L.

Results: The mean (SD) humidity at the Y-piece was 39.2 (5.2), 33.3 (4.1), and 36.7 (1.2) mg/L for 37-default, 33.5-theoretical, and 33.5-adjusted, respectively. The incidence of excessive high humidity was 10.3% (37-default, 31.0%; 33.5-theoretical, 0.0%; 33.5-adjusted, 0.0%), which was positively associated with the use of a counter-flow humidifier ($p<0.001$), 37-default (compared to 33.5-theoretical and 33.5-adjusted, both $p<0.001$) and higher fraction of inspired oxygen ($p=0.003$). The incidence of excessively low humidity was 17.5% (37-default, 7.1%; 33.5-theoretical, 45.2%; 33.5-adjusted, 0.0%), which was positively associated with 33.5-theoretical ($p<0.001$). All patients who used a counter-flow humidifier achieved the target gas humidity at the Y-piece (36.6+/-0.5mg/L) required for 33.5-adjusted with 33.5-theoretical.

Conclusions: During cooling, 37-default is associated with excessively high humidity, whereas 33.5-theoretical leads to excessively low humidity. Future studies are needed to assess whether a new regimen with optimised Y-piece temperature and humidity control reduces serious respiratory adverse events during cooling.

Key words:

Therapeutic hypothermia, mechanical ventilation, respiratory gases, temperature, humidity

Abbreviation list:

HFOV, high-frequency oscillation ventilation.

VAP, ventilator-associated pneumonia.

37-default, default humidifier setting under normothermia.

33.5-theoretical, theoretically adjusted humidifier setting for moderate hypothermia.

33.5-adjusted, adjusted humidifier setting to achieve the target Y-piece humidity/ temperature under moderate hypothermia.

Introduction

For mechanically ventilated patients, respiratory gases need to be appropriately heated and humidified to avoid complications, such as endotracheal tube obstruction and atelectasis(Restrepo and Walsh 2012; Williams *et al* 1996). Excessive humidification may also cause loss of mucosal function, airway oedema, and bronchial spasm(Pillow *et al* 2009; Sottiaux 2006; Williams *et al* 1996). The International Organization for Standardization recommends preparation of respiratory gases close to 100% humidity at 37°C (44mg/L), or at least to 75% of this level (33mg/L) during mechanical ventilation(ISO 8185:2007 Respiratory tract humidifiers for medical use. Particular requirements for respiratory humidification systems. 2007). To achieve this, respiratory gases are first passed into a humidifier or a temperature-controlled water bath, where the gases are humidified to the saturated vapour at 37°C(Yamada *et al* 2008). To prevent water condensation, the gases are then heated to 39–40°C while passing through a heated tube. Within the remaining part of the inspiratory circuit (i.e., extension tube and Y-piece) and the endotracheal tube, no active temperature control is provided, where gases are passively cooled to approximately 37°C.

Recently, therapeutic hypothermia to 32-34°C has been increasingly applied to patients with a range of cerebral injuries(Clifton *et al* 2011; Hutchison *et al* 2008; Jacobs *et al* 2013; Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest 2002; Todd *et al* 2005). These patients are generally under unstable cardiopulmonary conditions, most of whom require mechanical ventilation. Because saturated vapour is temperature-dependent, it reduces under hypothermic conditions (e.g., to 36.6mg/L at 33.5°C)(Sottiaux 2006). However, currently, a humidifier setting for normothermic conditions is recommended, even during therapeutic hypothermia(Lellouche *et al* 2006). Gas humidity of this level may be excessive for cooled patients, potentially causing significant water condensation and subsequent adverse events. Indeed, ventilator-associated pneumonia (VAP) is one of the most common reasons of mortality associated with therapeutic hypothermia in children and adults(Clifton *et al* 2011; Hutchison *et al* 2008; Todd *et al* 2005). Prevention of excessive humidification may improve the safety of cooling by reducing the incidence of VAP and other serious respiratory complications, and may increase the range of patients who have the benefit of cooling.

The aim of this study was to elucidate the incidence and independent variables of inappropriate Y-piece gas temperature and humidity in newborn infants, who are undergoing therapeutic hypothermia.

Methods

Methods are provided in detail in the Online Data Supplement (eText 1).

This study was conducted under the approval of the Ethics Committee of Kurume University School of Medicine (08069) with informed consent from substitute decision makers of the patients.

Study population

Between July 2011 and November 2014, 42 cumulative newborn infants (i.e. 24 patients were studied 42 times over different days) who were cooled to 33–34˚C at two tertiary neonatal intensive care units in Kurume, Fukuoka, Japan, were studied (Table 1). Data collection from the same patient was repeated only after major changes in ventilator settings, such as changes in mean airway pressure >5 cmH2O and changes in ventilation modes, with an interval of at least 24 hours.

Ventilators, circuits, and humidifiers

Five ventilators were used according to the availability and the patient's condition. We used ventilator-fixed humidifiers of either a pass-over humidifier (MR 730; Fisher and Paykel, Auckland, New Zealand) or a counter-flow humidifier(Schumann *et al* 2007) (Humicare 200; Gründler Medical, Freudenstadt, Germany) (Fig. 1 and eTable 1). Ventilator circuits were configured based on the manufacturer's recommendation, which were classified into those with short (≤10cm) or long (>10cm) non-heated extension tubes before the Y-piece (Fig. 1).

Data collection

Gases were assessed using a main-stream thermo-hygrometer (Moiscope, Skynet, Tokyo, Japan) that was placed between the extension tube and the Y-piece (Fig. 1). Temperature values at the humidifying chamber outlet ("chamber-outlet" temperature) and the distal end of the heated inspiratory circuit ("circuit" temperature) were provided by humidifying systems. The ambient and oesophageal temperatures were also recorded simultaneously. Data were collected for three humidifier settings as follow: (i) 37-default (default setting under normothermia; chamber-outlet, 37˚C; circuit, 40˚C), (ii) 33.5-theoretical (theoretically adjusted setting for moderate hypothermia; chamber-outlet, 33.5˚C; circuit, 36.5˚C), and (iii) 33.5-adjusted (settings were adjusted to achieve a temperature of 36.6 +/-0.5˚C and humidity of 36.6 +/-0.5mg/L or the closest values at the Y-piece). Each variable was recorded three times approximately every 3 minutes after chamber-outlet and circuit temperatures became stable. Patients' characteristics, treatments, and adverse events were observed from the clinical records.

Statistical analysis

Values are mean (SD) unless otherwise stated. Data were first compared between groups defined by the ventilation mode, ventilator circuit, and humidifier, using the Student's t-test (significance

assumed for $p<0.006$ correcting for eight comparisons). Associations between the ambient temperature, oesophageal temperature and Y-piece gas humidity/temperature were assessed using the linear regression analysis. Inappropriate Y-piece temperature/humidity was defined as follows: high temperature >38.5°C (i.e. 36.5 plus 2.0°C), low temperature <34.5°C (i.e. 36.5 minus 2.0°C), high humidity >40.7mg/L (saturated vapour at 35.5°C (i.e. 33.5 plus 2.0°C)), and low humidity <32.9mg/L (saturated vapour at 31.5°C (i.e. 33.5 minus 2.0°C)). These thresholds were defined based on clinical recommendations that Y-piece temperature should be controlled to +/-2°C from the target level(ISO 8185:2007 Respiratory tract humidifiers for medical use. Particular requirements for respiratory humidification systems. 2007). Independent variables of inappropriate Y-piece temperature/humidity were then assessed. Instead of repeating regression analyses over twelve combinations of datasets derived from four dependent variables and three humidifier settings, generalised estimating equations were used to evaluate the impact of each independent variable with adjustment for three humidifier settings (SPSS-21, IBM, New York, NY). Statistical significance for univariate analysis was assumed for $p<0.006$ correcting for eight comparisons. Independent variables for multivariate analysis were assigned by findings from univariate analysis and clinical relevance of the model.

Results

Clinical characteristics of patients

Data were successfully obtained from all 42 neonates, who were 38.3 (2.0) weeks gestation at birth and 1.2 (1.0) days old at the time of study. HFOV, counter-flow humidifiers and long extension tubes were used in 8, 8 and 25 patients, respectively. The mean airway pressure and the fraction of inspired oxygen were 8.3 (3.6) cmH_2O and 0.238 (0.059), respectively. The oesophageal temperature at the commencement of the study was 33.4 (0.3) °C, which remained at similar levels throughout the data collection. No relationship was observed between the ambient temperature, oesophageal temperature and Y-piece gas humidity/temperature.

Y-piece temperature and humidity for each humidifier setting (Fig. 2)

Setting of 37-default: Y-piece temperature and humidity were 37.1 (2.4)°C and 39.2 (5.2) mg/L, respectively. The Y-piece gas condition was similar between PTV and HFOV. Y-piece temperature and humidity were higher when counter-flow humidifiers (vs. pass-over humidifiers) and short extension tubes (vs. long extension tubes) were used (both $p<0.001$).

Setting of 33.5-theoretical: Y-piece temperature and humidity were 33.9 (2.5)°C and 33.3 (4.1) mg/L, respectively. Use of HFOV resulted in lower Y-piece temperature than PTV, whereas humidity was higher when counter-flow humidifiers were used (vs. pass-over humidifiers) (both $p<0.001$). Gas temperature was lower when long extension tubes were used than when short extension tubes were used ($p<0.001$).

Setting of 33.5-adjusted: Humidifier settings for the chamber-outlet and the circuit temperature were 36.5 (2.1)°C and 37.2 (1.4)°C, respectively, leading to Y-piece temperature and humidity of 34.9 (1.2)°C and 36.7 (1.2)mg/L, respectively. The humidifier setting at the circuit probe was lower when ventilated with PTV compared with HFOV, however, Y-piece temperature was higher with PTV than with HFOV (both p<0.001). When counter-flow humidifiers were used, the 33.5-theoretical setting provided sufficient temperature and humidity required for the 33.5-adjusted setting without adjustment. Although humidifier settings were lower at the chamber-outlet and circuit probes when counter-flow humidifiers were used than with pass-over humidifiers (p<0.001 and p=0.003, respectively), Y-piece humidity was higher with counter-flow humidifiers than with pass-over humidifiers (p<0.001). Humidifier settings were higher with long extension tubes than with short extension tubes for the chamber-outlet and circuit probes (both p<0.001). However, subsequent Y-piece temperature and humidity were lower with long extension tubes than with short extension tubes (both p<0.001).

Independent variables of inappropriate Y-piece temperature and humidity

High temperature >38.5°C (eTable 2A): Univariate analysis showed that the incidence of excessively high temperature was greater with the use of counter-flow humidifiers (p=0.004), short-extension tubes (p<0.001), and the 37-default setting (vs. 33.5-theoretical and 33.5-adjusted, both p<0.001). Multivariate analysis suggested that excessively high Y-piece gas temperature was associated with the use of short extension tubes and the 37-default setting (vs. 33.5-theoretical and 33.5-adjusted) (all p<0.001).

Low temperature <34.5°C (eTable 2B): Univariate analysis showed that the incidence of excessively low temperature was greater with the use of HFOV, pass-over humidifiers, long extension tubes, the 33.5-theoretical and 33.5-adjusted settings (vs. 37-default), and a higher mean airway pressure (all p<0.001). Multivariate analysis showed that excessively low temperature was positively associated with the use of HFOV (P=0.038), long extension tubes (p<0.001), and the 33.5-theoretical and 33.5-adjusted settings (vs. 37-default, both p<0.001).

High humidity >40.7 mg/L (Table 2A): Univariate analysis showed that observation of excessively high humidity was greater with the use of counter-flow humidifiers (p=0.001) and the 37-defautl setting (vs. 33.5-theoretical and 33.5-adjusted, both p<0.001). Multivariate analysis showed that short extension tubes (p=0.003), the 37-defautl setting (vs. 33.5-theoretical and 33.5-adjusted, both p<0.001), and a higher constant flow (p<0.001) were associated with a greater risk of excessively high humidity.

Low humidity <32.9mg/L (Table 2B): Univariate analysis showed that the risk of excessively low humidity was greater with the use of pass-over humidifiers and the 33.5-theoretical setting (vs. 37-default) (both p<0.001). Multivariate analysis revealed that the risk of excessively low humidity was associated with the use of pass-over humidifiers and the 33.5-adjusted setting (vs. 37-default) (both p<0.001).

Clinical adverse events: All of the patients survived to discharge. Two newborn infants developed septicaemia during cooling, whose blood cultures at admission (i.e., before cooling) were positive (Table 1). A newborn infant experienced endo-tracheal tube obstruction, in whom extremely low humidity was confirmed with the 37-default and 33.5-theoretical settings when studied after re-intubation.

Discussion

In our study, during therapeutic hypothermia, the use of a default humidifier setting for normothermia increased the risks for excessively high Y-piece gas temperature and humidity. The humidifier setting that was theoretically adjusted for body temperature was associated with an increased incidence of excessively low Y-piece gas temperature and humidity. In addition to humidifier settings, types of humidifying systems and inspiratory circuits, and the constant flow of the ventilator were identified as important independent variables of inappropriate gas humidification. To deliver appropriately humidified gases to hypothermic patients, humidifier settings need to be adjusted with the feedback from Y-piece hygrometer readings; or, alternatively, a counter-flow humidifier can be used with a theoretically body-temperature-adjusted setting.

Problems of the default humidifier setting for normothermia during cooling

International guidelines of resuscitation currently recommend cooling severely asphyxiated newborn infants and adult patients following cardiac arrest(Peberdy *et al* 2010; Perlman *et al* 2010). This has resulted in an increasing number of patients undergoing therapeutic hypothermia(Azzopardi *et al* 2012; Dankiewicz *et al* 2014; Iwata *et al* 2014; Nelson *et al* 2012). Although the safety and efficacy of whole-body cooling to 33.5°C for 72 hours have been established in newborn infants(Jacobs *et al* 2013), therapeutic hypothermia only has a narrow margin of benefit in child and adult patients due in part to high mortality associated with serious systemic and respiratory complications(Clifton *et al* 2011; Hutchison *et al* 2008; Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest 2002; Todd *et al* 2005). In our study, we showed that the currently recommended humidifier setting led to a considerable incidence of excessive heating (35.7%) and humidification (31.0%). Current humidifying systems generally provide only modest humidity as opposed to the ideal level(Al Ashry and Modrykamien 2014; Pelosi *et al* 2007). Therefore, we rarely encounter excessive humidity during ventilation. However, saturated vapour differs by 4.0mg/L between 33.5˚C and 35.5˚C. When a hypothermic patient of 3.5kg is ventilated using the 37.0-default setting, approximately 8mL of water is delivered to the airway per day, assuming that the tidal volume is 8mL/kg and the respiratory rate is 50 breaths/minute. Unlike isotonic fluids, distilled water of this volume may cause airway oedema, bronchial spasms, and mucosal dysfunction(Pillow *et al* 2009; Sottiaux 2006; Williams *et al* 1996; Williams 1998). Improved humidification of respiratory gases may significantly ameliorate respiratory complications of patients who undergo therapeutic hypothermia.

Pitfalls of the theoretical body temperature-adjusted humidifier setting

In our study, use of the 33.5-theoretical setting resulted in a considerable incidence of excessively low temperature (54.8%) and humidity (45.2%). This finding might be explained by the above-mentioned trend of currently available humidifying systems, which are generally under-powered(Al Ashry and Modrykamien 2014; Pelosi *et al* 2007). The use of long extension

tubes may further reduce Y-piece temperature and humidity(Todd *et al* 2001). Long extension tubes are used to minimise the effect of a relatively high ambient temperature within closed incubators. However, because even newborn infants are usually cooled in an open incubator(Azzopardi *et al* 2009; Gluckman *et al* 2005; Iwata *et al* 2012), long extension tubes might merely be harmful. In addition, significant changes in the performance of pass-over humidifiers have been reported when the temperature difference of gases between the inlet and outlet of the humidifying chamber becomes small(Carter *et al* 2002; Lellouche *et al* 2004). When the chamber-inlet temperature is already close to the target level (e.g., 37˚C), the humidifier turns off its heater, where only the target temperature, but not the target humidity, is achieved at the chamber-outlet. Such a phenomenon may also be yielded by a lowered target gas temperature at the chamber-outlet, as with the 33.5-theoretical setting.

Current solutions to optimise humidity of respiratory gases under hypothermia

Our data suggested that the counter-flow humidifier is likely to provided perfect temperature/humidity control during cooling. However, considering the relatively more expensive price of counter-flow humidifiers, alternative solutions are necessary. In the current study, when the humidifier setting was adjusted by obtaining feedback from Y-piece gas monitoring, excessively high and low humidification was totally eliminated. Consistent to previous findings in normothermic patients(Chikata *et al* 2009; Pelosi *et al* 2007), Y-piece temperature/humidity depended on ventilation mode and constant flow of the ventilator even in cooled patients. Further studies are required to specify independent variables of inappropriate humidification.

Limitations

Our study population is too small to determine all of the problems and their solutions. The pass-over humidifier that was used in our study (MR 730) has since been replaced by a new fully automated model (MR 850), which does not allow manual adjustment of the chamber outlet and circuit temperatures, leading to difficulty in avoiding excessively high humidity in hypothermic patients. We assumed a temperature reduction of respiratory gasses within the endotracheal tube as approximately 3˚C regardless of the target Y-piece temperature, which might be different under cooling. We defined an “inappropriate Y-piece temperature/humidity” based on the statement by the International Organization for Standardization(ISO 8185:2007 Respiratory tract humidifiers for medical use. Particular requirements for respiratory humidification systems. 2007), which might be different from the actual threshold humidity levels associated with clinical adverse events.

Conclusions

Neither the default setting for normothermia nor the theoretically adjusted setting for hypothermia provides optimal Y-piece temperature and humidity during therapeutic hypothermia. To prevent inappropriate humidification, temperature and humidity of respiratory gases need to be monitored and adjusted. Alternatively, a counter-flow humidifier might be used with a theoretically adjusted setting. Independent variables that are associated with inappropriate Y-piece temperature and humidity, such as the use of long-extension tubes and relatively high constant flow of ventilators, should be avoided. Future studies need to assess whether a new regimen with optimal Y-piece temperature and humidity control reduces serious respiratory complications associated with therapeutic hypothermia in a wide age range of patients. Finally, an additional mode for hypothermic patients' needs to be urgently developed for fully automated humidifiers.

Acknowledgements

The authors thank Profs Toyojiro Matsuishi and Masanori Tamura for their useful advice, Drs Hiroki Saitsu, Mitsuaki Unno, Akiko Hirose and Hiroshi Kanda, Mr Ryouji Kijima, Mr Osamu Yamaga, and Mr Shintaro Tomonaga, and Ms Chiho Yoshii, for their assistance in data collection.

Author Disclosure Statement:

The authors have indicated that they have no financial relationships relevant to this article to disclose.

Funding source and role:

This work was supported by the Japanese Ministry of Health, Labour and Welfare (H27-001, Special research in perinatal medicine). Dr Iwata O is also funded by the Japan Science and Technology Agency and the Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for Scientific Research B01-24119004, Constructive Developmental Science, Innovative Areas). Dr Iwata S is funded by the Japan Science and Technology Agency and the Ministry of Education, Culture, Sports, Science and Technology (Grant-in-Aid for Scientific Research C24591533).

References

Al Ashry HS, Modrykamien AM (2014) Humidification during mechanical ventilation in the adult patient. *BioMed research international* 2014:715434

Azzopardi D, Strohm B, Linsell L, Hobson A, Juszczak E, Kurinczuk JJ, Brocklehurst P, Edwards AD (2012) Implementation and conduct of therapeutic hypothermia for perinatal asphyxial encephalopathy in the UK--analysis of national data. *PloS one* 7:e38504

Azzopardi DV, Strohm B, Edwards AD, Dyet L, Halliday HL, Juszczak E, Kapellou O, Levene M, Marlow N, Porter E, Thoresen M, Whitelaw A, Brocklehurst P (2009) Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 361:1349-58

Carter BG, Whittington N, Hochmann M, Osborne A (2002) The effect of inlet gas temperatures on heated humidifier performance. *Journal of aerosol medicine : the official journal of the International Society for Aerosols in Medicine* 15:7-13

Chikata Y, Imanaka H, Onishi Y, Ueta M, Nishimura M (2009) Humidification during high-frequency oscillation ventilation is affected by ventilator circuit and ventilatory setting. *Paediatr Anaesth* 19:779-83

Clifton GL, Valadka A, Zygun D, Coffey CS, Drever P, Fourwinds S, Janis LS, Wilde E, Taylor P, Harshman K, Conley A, Puccio A, Levin HS, McCauley SR, Bucholz RD, Smith KR, Schmidt JH, Scott JN, Yonas H, Okonkwo DO (2011) Very early hypothermia induction in patients with severe brain injury (the National Acute Brain Injury Study: Hypothermia II): a randomised trial. *Lancet Neurol* 10:131-9

Dankiewicz J, Schmidbauer S, Nielsen N, Kern KB, Mooney MR, Stammet P, Riker RR, Rubertsson S, Seder D, Smid O, Sunde K, Soreide E, Unger BT, Friberg H (2014) Safety, feasibility, and outcomes of induced hypothermia therapy following in-hospital cardiac arrest-evaluation of a large prospective registry*. *Crit Care Med* 42:2537-45

Gluckman PD, Wyatt JS, Azzopardi D, Ballard R, Edwards AD, Ferriero DM, Polin RA, Robertson CM, Thoresen M, Whitelaw A, Gunn AJ (2005) Selective head cooling with mild systemic hypothermia after neonatal encephalopathy: multicentre randomised trial. *Lancet* 365:663-70

Hutchison JS, Ward RE, Lacroix J, Hebert PC, Barnes MA, Bohn DJ, Dirks PB, Doucette S, Fergusson D, Gottesman R, Joffe AR, Kirpalani HM, Meyer PG, Morris KP, Moher D, Singh RN, Skippen PW (2008) Hypothermia therapy after traumatic brain injury in children. *NEnglJ Med* 358:2447-56

ISO 8185:2007 Respiratory tract humidifiers for medical use. Particular requirements for respiratory

humidification systems. (2007). http://wwwisoorg/iso/catalogue_detailhtm?csnumber=38527

Iwata O, Nabetani M, Takenouchi T, Iwaibara T, Iwata S, Tamura M (2012) Hypothermia for neonatal encephalopathy: Nationwide Survey of Clinical Practice in Japan as of August 2010. *Acta Paediatr* 101:e197-202

Iwata O, Takenouchi T, Iwata S, Nabetani M, Mukai T, Shibasaki J, Tsuda K, Tokuhisa T, Sobajima H, Tamura M (2014) The baby cooling project of Japan to implement evidence-based neonatal cooling. *Therapeutic hypothermia and temperature management* 4:173-9

Jacobs SE, Berg M, Hunt R, Tarnow-Mordi WO, Inder TE, Davis PG (2013) Cooling for newborns with hypoxic ischaemic encephalopathy. *Cochrane Database Syst Rev* 1:CD003311

Lellouche F, Taille S, Maggiore SM, Qader S, L'Her E, Deye N, Brochard L (2004) Influence of ambient and ventilator output temperatures on performance of heated-wire humidifiers. *American journal of respiratory and critical care medicine* 170:1073-9

Lellouche F, Qader S, Taille S, Lyazidi A, Brochard L (2006) Under-humidification and over-humidification during moderate induced hypothermia with usual devices. *Intensive Care Med* 32:1014-21

Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest (2002). *NEnglJ Med* 346:549-56

Nelson KB, Bingham P, Edwards EM, Horbar JD, Kenny MJ, Inder T, Pfister RH, Raju T, Soll RF (2012) Antecedents of neonatal encephalopathy in the Vermont Oxford Network Encephalopathy Registry. *Pediatrics* 130:878-86

Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL, Kronick SL (2010) Part 9: post-cardiac arrest care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation* 122:S768-86

Pelosi P, Chiumello D, Severgnini P, De Grandis CE, Landi L, Chierichetti LM, Frigerio A, Munaro M, Park G, Chiaranda M (2007) Performance of heated wire humidifiers: an in vitro study. *Journal of critical care* 22:258-64

Perlman JM, Wyllie J, Kattwinkel J, Atkins DL, Chameides L, Goldsmith JP, Guinsburg R, Hazinski MF,

Morley C, Richmond S, Simon WM, Singhal N, Szyld E, Tamura M, Velaphi S (2010) Part 11: neonatal resuscitation: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation* 122:S516-38

Pillow JJ, Hillman NH, Polglase GR, Moss TJ, Kallapur SG, Cheah FC, Kramer BW, Jobe AH (2009) Oxygen, temperature and humidity of inspired gases and their influences on airway and lung tissue in near-term lambs. *Intensive Care Med* 35:2157-63

Restrepo RD, Walsh BK (2012) Humidification during invasive and noninvasive mechanical ventilation: 2012. *Respiratory care* 57:782-8

Schumann S, Stahl CA, Moller K, Priebe HJ, Guttmann J (2007) Moisturizing and mechanical characteristics of a new counter-flow type heated humidifier. *Br J Anaesth* 98:531-8

Sottiaux TM (2006) Consequences of under- and over-humidification. *Respiratory care clinics of North America* 12:233-52

Todd DA, Boyd J, Lloyd J, John E (2001) Inspired gas temperature during mechanical ventilation: effects of environmental temperature and airway temperature probe position. *Journal of paediatrics and child health* 37:495-500

Todd MM, Hindman BJ, Clarke WR, Torner JC (2005) Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med* 352:135-45

Williams R, Rankin N, Smith T, Galler D, Seakins P (1996) Relationship between the humidity and temperature of inspired gas and the function of the airway mucosa. *Crit Care Med* 24:1920-9

Williams RB (1998) The effects of excessive humidity. *Respiratory care clinics of North America* 4:215-28

Yamada Y, Kyuno T, Suzuki S, Ito T, Kato I, Togari H (2008) A drop in gas temperature in the external part of the endotracheal tube is problematic during neonatal respiratory support. *Pediatr Pulmonol* 43:666-73

Tables

Table 1: Clinical background variables of the study population.

Overall study cohort		24 (42*)
Institution	Kurume	15 (28*)
	St Mary's	9 (14*)
Sex (female)		7 (29.2%)
Age		1 (0–3) days
Body weight (kg)		2.7 (1.8–4.5)
Ventilator	840	9*
	Baby Log 800 plus	4*
	Baby Log VN500	4*
	SLE 5000	10*
	Humming Bird V	15*
Ventilator mode	PTV/HFOV	34*/8*
Type of humidifier	Counter-flow/pass-over	8*/34*
Non-heated extension	Long/short	25*/17*
Constant flow of ventilator (L/min)	Mean (SD)	6.3 (3.5)
Mean airway pressure (cmH_2O)	Mean (SD)	8.3 (3.6)
Fraction of inspired oxygen	Mean (SD)	0.238 (0.059)
Oesophageal temperature (°C)	Mean (SD)	33.4 (0.3)
Ambient temperature (°C)	Mean (SD)	27.1 (1.4)
Size of endotracheal tube (mm)		3.0 (3.0–3.5)
Adverse events	Tube obstruction	1
	Pneumothorax	2
	VAP	1
	Septicaemia	2
	Death	0
Days on ventilator		12.7 (1–24)

Values are shown as number (*cumulative) or median (range) unless otherwise specified.
Abbreviations: HFOV, high-frequency oscillatory ventilation; PTV, patient-triggered ventilation; VAP, ventilator-associated pneumonia.

Table 2: Independent variables of inappropriate gas humidity.

A: High humidity

Univariate model		Y-piece humidity > 40.7mg/L				B (Wald type 95% CI)			P
		Yes (n = 13)		No (n = 113)		Mean	Lower	Upper	
Categorical variables		n	%	n	%				
Ventilation mode	PTV	11	10.5	94	89.5	0.01	-0.12	0.14	0.882
	HFOV	2	9.5	19	90.5	Reference			
Type of humidifier	Pass-over	7	6.9	95	93.1	-0.18	-0.29	-0.07	0.001
	Counter-flow	6	25.0	18	75.0	Reference			
Non-heated extension	Short	8	15.7	43	84.3	0.09	0.00	0.18	0.055
	Long	5	6.7	70	93.3	Reference			
Humidifier setting	37-default	13	31.0	29	69.0	Reference			
	33.5-theoretical	0	0.0	42	100.0	-0.31	-0.45	-0.17	< 0.001
	33.5-adjusted	0	0.0	42	100.0	-0.31	-0.45	-0.17	< 0.001
Numeric variables		Mean (95% CI)		Mean (95% CI)					
Constant flow of ventilator (L/min.)		8.0 (6.5, 9.5)		6.1 (5.4, 6.7)		0.02	0.00	0.03	0.016
Mean airway pressure (cmH_2O)		8.2 (6.5, 10.0)		8.3 (7.7, 9.0)		0.00	-0.01	0.01	0.929
Fraction of inspired oxygen		0.27 (0.22, 0.31)		0.23 (0.23, 0.24)		0.85	0.20	1.51	0.011
Ambient temperature (^oC)		26.8 (26.3, 27.4)		27.1 (26.8, 27.4)		-0.01	-0.04	0.02	0.388

Multivariate model		B (Wald type 95% CI)			P
		Mean	Lower	Upper	
Non-heated extension	Short	0.12	0.04	0.2	0.003
	Long	Reference			
Humidifier setting	37-default	Reference			
	33.5-theoretical	-0.31	-0.45	-0.17	< 0.001
	33.5-adjusted	-0.31	-0.45	-0.17	< 0.001
Constant flow of ventilator (L/min.)		0.02	0.01	0.03	< 0.001

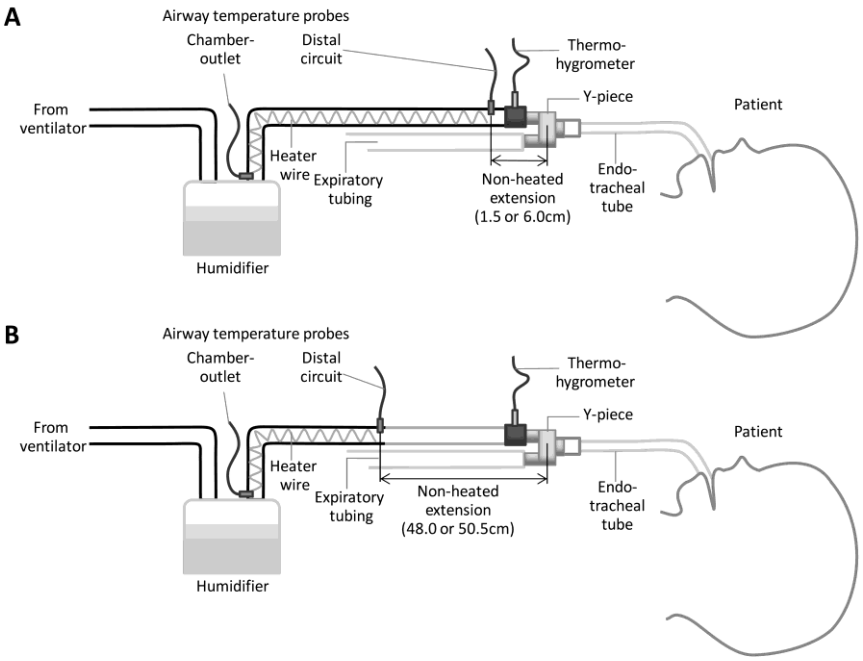
B: Low humidity

Univariate model		Y-piece humidity < 32.9mg/L				B (Wald type 95% CI)			P
		Yes (n = 22)		No (n = 104)		Mean	Lower	Upper	
Categorical variables		n	%	n	%				
Ventilation mode	PTV	18	17.1	87	82.9	-0.02	-0.19	0.15	0.826
	HFOV	4	19.0	17	81.0	Reference			
Type of humidifier	Pass-over	22	21.6	80	78.4	0.22	0.14	0.29	< 0.001
	Counter-flow	0	0.0	24	100.0	Reference			
Non-heated extension	Short	6	11.8	45	88.2	-0.1	-0.23	0.03	0.149
	Long	16	21.3	59	78.7	Reference			
Humidifier setting	37-default	3	7.1	39	92.9	Reference			
	33.5-theoretical	19	45.2	23	54.8	0.38	0.23	0.53	< 0.001
	33.5-adjusted	0	0.0	42	100.0	-0.07	-0.15	0.01	0.072
Numeric variables		Mean (95% CI)		Mean (95% CI)					
Constant flow of ventilator (L/min.)		5.1 (3.6, 6.6)		6.5 (5.9, 7.2)		-0.02	-0.04	0.00	0.051
Mean airway pressure (cmH_2O)		8.1 (6.6, 9.7)		8.3 (7.7, 9.0)		0.00	-0.02	0.02	0.810
Fraction of inspired oxygen		0.22 (0.21, 0.24)		0.24 (0.23, 0.25)		-0.72	-1.48	0.04	0.065
Ambient temperature (^oC)		27.3 (26.6, 28)		27.0 (26.8, 27.3)		0.02	-0.04	0.08	0.500
Multivariate model						B (Wald type 95% CI)			P
						Mean	Lower	Upper	
Type of humidifier	Pass-over					0.22	0.14	0.29	< 0.001
	Counter-flow					Reference			
Humidifier setting	37-default					Reference			
	33.5-theoretical					0.38	0.23	0.53	< 0.001
	33.5-adjusted					-0.07	-0.15	0.01	0.074

Abbreviations: HFOV, high-frequency oscillatory ventilation; PTV, patient-triggered ventilation.

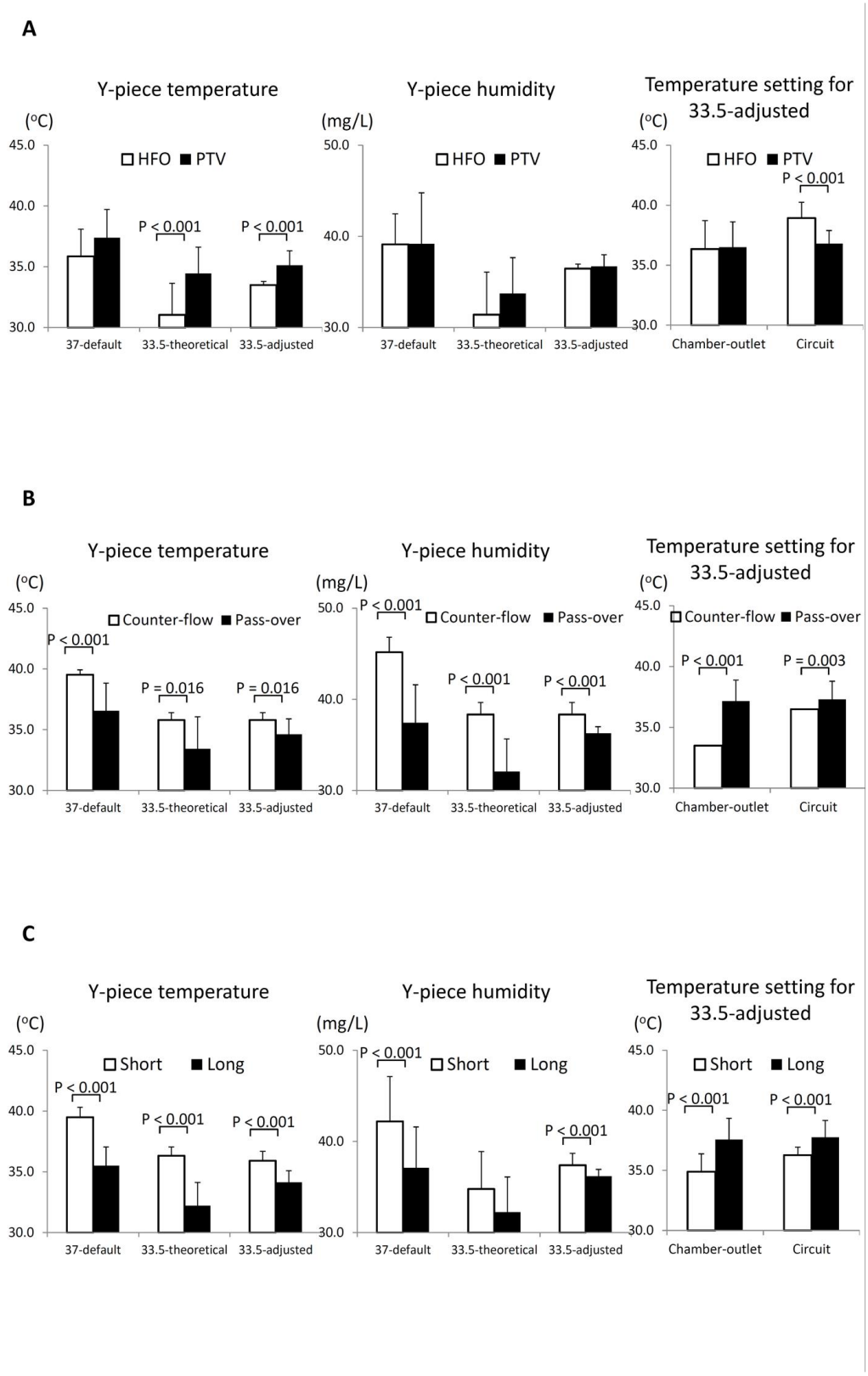
Figure legends

Figure 1: Configurations of humidifying systems and ventilator circuits.



Humidifying system and ventilator circuit with short (A) and long (B) non-heated extension part/tubes. The length between the circuit temperature probe and the centre of the Y-piece was measured with the thermo-hygrometer disconnected.

Figure 2: Effect of ventilation modes and humidifying systems on Y-piece gas conditions.



A: High-frequency oscillatory ventilation vs. patient-triggered ventilation

Y-piece temperature was higher with PTV than with HFOV for the 33.5-theoretical and 33.5-adjusted settings (both p<0.001), but Y-piece humidity was similar between the two ventilation modes. For 33.5-adjusted, HFOV required a higher humidifier setting at the circuit probe (p<0.001) compared with PTV.

B: Pass-over vs. counter-flow humidifiers

Y-piece temperature was higher for 37-default when a counter-flow humidifier was used compared with a pass-over humidifier (p<0.001, not significant for 33.5-theoretical and 33.5-adjusted when corrected for multiple comparisons). Y-piece humidity was higher with a counter-flow humidifier compared with a pass-over humidifier for all three humidifier settings (all p<0.001). When a counter-flow humidifier was used, the 33.5-theoretical setting provided sufficient temperature and humidity required for 33.5-adjusted without adjustment. This resulted in a lower chamber outlet temperature settings with a counter-flow humidifier than with a pass-over humidifier at the chamber-outlet probe (p<0.001) and the circuit probe (p=0.003).

C: Short or long non-heated extension tubes

The use of long extension tubes led to a lower gas temperature compared with short extension tubes for all three humidifier settings (all p<0.001). Y-piece humidity was lower with a long extension tube than with a short extension tube for 37-default and 33.5-adjusted (both p<0.001, not significant for 33.5-theoretical). The humidifier setting for 33.5-adjusted was higher with a long extension tube than with a short extension tube for the chamber-outlet and the circuit probe (both p<0.001).

Statistical significance was assumed for p<0.006 (Bonferroni-corrected for eight comparisons).
Abbreviations: HFOV, high-frequency oscillatory ventilation. PTV, patient-triggered ventilation.