



A Comparison of the Effects of Lung Protective Ventilation and Conventional Ventilation on Thermoregulation During Anaesthesia

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Abstract

Objective: During prolonged surgery, hypothermia is an unwanted condition that frequently develops and increases complication rates. It has been shown that positive end-expiratory pressure (PEEP) during mechanical ventilation reduces hypothermia development by providing earlier peripheral vasoconstriction. In the present study, an investigation was made of the effect of two different ventilation models on perioperative hypothermia development.

Methods: A total of 40 patients undergoing elective lumbar disc surgery were randomised to either the conventional group (Group C, n=20, tidal volume=10 mL kg⁻¹, PEEP=0 cm H₂O) or the lung protective ventilation group (Group P, n=20, tidal volume=6 mL kg⁻¹, PEEP=5 cm H₂O). Demographic data on gender, age, weight, height, preoperative–postoperative temperatures and haemodynamic values were recorded. The point where the forearm to fingertip skin temperature difference reached 0°C was determined as the peripheral vasoconstriction development. At this point, the core temperature was recorded as the thermoregulatory vasoconstriction threshold.

Results: Demographic characteristics of the patients and haemodynamic variables were similar between the groups. Preoperative and postoperative temperature gradients were not significantly different between the two groups (p=0.827). There was also no significant difference between the two groups in respect of the vasoconstriction threshold of the patients (p=0.432).

Conclusion: The study results showed that lung protective ventilation has no advantage in preserving the perioperative core temperature compared to conventional ventilation.

Keywords: Lung protective ventilation, thermoregulation, vasoconstriction threshold

Introduction

Body temperature is controlled by the hypothalamus. This control mechanism is suppressed in patients under anaesthesia, and body temperature decreases. This effect is observed even in patients under sedation. One of the important factors in decreasing body temperature is the heat distribution to the periphery from the centre. The response of the body to this heat distribution is peripheral vasoconstriction, and this response mechanism is suppressed in a dose-dependent manner in patients undergoing general anaesthesia (1).

Under general anaesthesia, approximately 10% of heat loss is through heating and humidifying airways. Inhalation of cold anaesthetic gases without heat and moisture exchangers and high-minute ventilation can increase heat loss. The effect of heat loss becomes even more significant in long operations and can cause postoperative complications, leading to increased cost, mortality and morbidity (2-5).

In conventional mechanical ventilation, patients are ventilated with high-tidal volume without applying positive end-expiratory pressure (PEEP). Approximately 10-12 mL kg⁻¹ tidal volume allows the alveoli to open and improves gas exchange but also leads to ventilation-induced lung injury. For lung protective ventilation, lower tidal volumes with PEEP are used. This type of ventilation reduces lung trauma, but there is the risk of hypoventilation. Therefore, both ventilation types have both benefits and risks (6, 7). In addition, PEEP application in patients under general anaesthesia has been shown to reduce heat loss by providing baroreceptor unloading that augments the peripheral vasoconstriction and catecholamine response to core hypothermia while simultaneously reducing thermogenesis, and via baroreceptor unloading, earlier peripheral vasoconstriction increases the vasoconstriction threshold while increasing central blood volume (8-10).

The aim of the present study was to compare the effects of conventional mechanical ventilation and lung protective ventilation on thermoregulatory responses.

Methods

The ethics committee of Afyon Kocatepe University School of Medicine approved the study (no. 58, 11/11/2016). Written informed consent was obtained from each patient who participated in the study. A total of 40 patients with an American Society of Anesthesiologists physical status of I-II, aged 20-60 years and undergoing elective lumbar disc surgery were enrolled in the study. Patients with diabetes mellitus, peripheral vascular disease, such as Raynaud's disease, vasoactive drug use, thyroid disease; who were using drugs that could affect the cardiovascular system and who were obese were excluded from the study. Patients were also excluded if the operation was <60 min and if there was a need for vasoactive drugs.

Patients were randomised to either the conventional group (Group C, n=20) or the lung protective ventilation group (Group P, n=20) using a sealed envelope system.

Patients were not premedicated and were prepared to undergo operation with a minimum body temperature of 36°C. The operating room temperature was maintained at 22°C-24°C. Upon arrival in the operating room, standard anaesthesia monitoring was applied including non-invasive blood pressure, pulse oximetry, electrocardiography and capnography.

Anaesthesia was induced using 2 mg kg⁻¹ propofol and 2 µg kg⁻¹ fentanyl. Intubation was facilitated using 0.6 mg kg⁻¹ rocuronium. Maintenance of anaesthesia was provided by 1 MAC fentanyl and desflurane to maintain the bispectral in-

dex value between 40 and 60. All patients were ventilated by an S15 Avance anaesthesia machine (GE Healthcare, Madison, WI, USA). Patients were randomised into two groups according to the ventilator settings: conventional (C) and lung protective (P) groups. A 10 mL kg⁻¹ VT (according to the ideal height and weight of the patients) and a 0 cm H₂O PEEP were applied to the patients in Group C, and a 6 mL kg⁻¹ VT (according to the ideal weight of the patients) and a 5 cm H₂O PEEP were applied to the patients in Group P. The ideal body weight of the patients was estimated using the following formula: $45.5 \pm 0.91 \times (\text{cm of height} - 152.4)$ (11). The respiratory rate was adjusted to maintain the end-tidal carbon dioxide levels between 35 and 40 mmHg.

After anaesthesia induction, three temperature probes were placed, one in the oesophagus, one at the forearm and one at the fingertip. Patients were covered with a sheet of surgical drape, and no additional heating was applied. The point where the forearm to finger skin temperature difference reached 0 °C was set as the peripheral vasoconstriction development. At this point, the core temperature was recorded as the thermoregulatory vasoconstriction threshold.

Demographic data of the patients, length of surgery and total amount of fluid given were recorded. Measurements of mean arterial pressures (MAPs), heart rates (HRs) and preoperative and postoperative temperatures were recorded. The thermoregulatory responses of the groups were compared in respect of the number of patients with peripheral vasoconstriction, peripheral vasoconstriction thresholds and mean temperature loss during the operation.

Statistical analysis

Power analysis was conducted using the G Power 3.1.9.2 package program to determine the number of observations based on an original research article (12) in the literature by analysing the vasoconstriction thresholds and core temperature gradient, and the size of the sample required was determined as 16, with effect size=0.5 (medium), $\alpha=0.05$ and power=95%. Since vasoconstriction may not develop in every patient, the number of patients was increased to obtain more reliable results as the number of samples increases. The IBM Statistical Package for the Social Sciences version 20.0 software (IBM SPSS Corp.; Armonk, NY, USA) was used for statistical analyses. Conformity of the data to normal distribution was assessed by the one-sample Kolmogorov-Smirnov test. Data were expressed as mean±standard deviation or number (n) and percentage (%) when appropriate. Comparisons between the groups were made using the Student's t-test or Mann-Whitney U test as appropriate. The Fisher's exact test or the chi-square test was used to assess group differences for categorical variables. A p-value <0.05 was considered statistically significant.

Results

A total of 20 patients were included in each group, and all completed the study. Patient characteristics, duration of anaesthesia and surgery were similar between the groups (Table 1). There were no significant differences between the groups in fluid intake during surgery or in perioperative haemoglobin values (p=0.694, Table 1).

There was no statistically significant difference between the groups at any of the perioperative measurement times of the haemodynamic parameters (MAP and HR, Tables 2, 3).

The operating room temperature was between 22°C and 24°C in both groups, with no significant difference determined at pre-induction, 30 min, 90 min and post-operation, respectively (p=0.705, p=0.130, p=0.630 and p=0.837, respectively, Table 4).

There was no significant difference in preoperative and postoperative temperatures (core, forearm and peripheral) between the groups, respectively (core preoperative: p=0.881, postoperative: p=0.446, forearm preoperative: p=0.201, postoperative: p=0.056, peripheral preoperative: p=0.550 and postoperative: p=0.070, Table 5).

Table 1. Demographic, anaesthetic and operation characteristics

	Group P (n=20)	Group C (n=20)	p
Gender (F/M), n	11/9	8/12	0.902
Age (year)	55.5±6.78	54.95±7.51	0.839
Height (cm)	165.3±5.30	162.85±6.79	0.184
Weight (kg)	78.35±6.78	76.65±7.30	0.416
Body mass index (kg m ⁻²)	28.97±2.98	28.72±2.72	0.704
Total fluid replacement (mL)	1586±287	1602±283	0.776
Mean preoperative haemoglobin (g L ⁻¹)	12.63±1.43	12.78±1.49	0.694
Anaesthesia time (min)	142.3±26.82	150±20.02	0.546
Surgery time (min)	161.25±19.02	167±15.40	0.362

Values are presented as mean±SD. There were no statistically significant differences between the groups.
Group P: protective ventilation group, Group C: conventional ventilation group. F: female; M: male

Table 2. MBP values according to groups

MBP values (mm Hg)	Group P (n=20)	Group C (n=20)	p
Preoperation	108.04±14.53	105.96±15.29	0.799
15 min	90.0±18.45	76.82±9.36	0.758
30 min	89.28±12.58	77.06±17.76	0.968
60 min	85.1±15.88	84.56±15.88	0.512
90 min	85.16±15.80	87.56±17.67	0.602
120 min	88.13±13.39	86.04±14.44	0.565
150 min	89.8±12.12	89.5±14.52	0.961
180 min	101±10.58	94.5±19.09	0.177

Values are presented as mean±SD. There were no statistically significant differences between the groups.
Group P: protective ventilation group, Group C: conventional ventilation group, MBP: mean blood pressure

Table 3. Heart rate values of the groups

Heart rate (beats min ⁻¹)	Group P (n=20)	Group C (n=20)	p
Pre-induction	94.45±12.9	83.0±18.07	0.084
15 min	91.5±11.35	79.8±16.88	0.072
30 min	86.95±11.97	76.05±13.44	0.060
45 min	82.55±8.66	76.15±10.52	0.790
60 min	80.10±8.32	73.65±7.86	0.070
75 min	79.60±8.72	72.6±8.08	0.081
90 min	78.80±8.61	72.25±8.68	0.082
105 min	77.55±8.57	73.65±6.69	0.085
120 min	78.95±8.64	75.30±6.54	0.059
135 min	82.20±10.73	76.21±7.91	0.091
150 min	80.78±8.34	76±6.37	0.087
165 min	87.68±12.08	79.92±10.26	0.104
180 min	95.00±16.24	83.45±9.95	0.114

Values are presented as mean±SD. There were no statistically significant differences between the groups.
Group P: protective ventilation group, Group C: conventional ventilation group

Table 4. Operating room temperatures

Temperature (°C)	Group P (n=20)	Group C (n=20)	p
Pre-induction	21.03±0.56	20.97±0.54	0.705
30 min	21.05±0.50	20.91±0.64	0.130
90 min	21.26±0.57	21.35±0.55	0.630
Post-operation	20.93±0.40	20.90±0.43	0.837

Values are presented as mean±SD. There were no statistically significant differences between the groups.
Group P: protective ventilation group, Group C: conventional ventilation group

Temperature (°C)	Group P (n=20)	Group C (n=20)	p
Core temperature preoperative	36.19±0.88	36.36±0.22	0.881
Core temperature postoperative	35.07±0.38	35.06±0.59	0.446
Forearm temperature preoperative	33.51±0.40	33.31±0.62	0.201
Forearm temperature postoperative	31.98±0.73	31.31±0.76	0.056
Peripheral temperature preoperative	33.22±0.73	33.08±0.70	0.550
Peripheral temperature postoperative	31.51±0.72	30.54±0.84	0.070

Values are presented as mean±SD. There were no statistically significant differences between the groups. Group P: protective ventilation group, Group C: conventional ventilation group.

	Group P (n=20)	Group C (n=20)	p
Patients with vasoconstriction, n	12	9	0.337
Vasoconstriction threshold (°C)	35.53±29	35.4±0.36	0.432
Intraoperative vasoconstriction time (min)	89.0±22.7	102.0±32.6	0.298
Core temperature gradient (°C)	1.12±0.87	1.29±0.37	0.827

Values are presented as mean±SD. There were no statistically significant differences between the groups. Group P: protective ventilation group, Group C: conventional ventilation group.

There was no significant difference between the groups in respect of the number of patients where vasoconstriction occurred ($p=0.337$), neither was there any difference in vasoconstriction thresholds ($p=0.432$) and core temperature gradient ($p=0.827$, Table 6). In addition, intraoperative vasoconstriction time was similar between the groups ($p=0.298$, Table 6).

Balanced crystalloid solutions were used in the maintenance of fluid therapy. Blood transfusion was not required for any of the patients.

Discussion

Perioperative unintended hypothermia is an unwanted condition where the temperature of the patient decreases to $<36^{\circ}\text{C}$ in 1 h before and 24 h after the operation (13). The severity of hypothermia is directly affected by the gender or age of the patient, type of anaesthesia used, duration of the operation and use of mechanical ventilation. Many reasons for hypothermia have been investigated in the literature, but there has been insufficient research on the effects of mechanical ventilation mode on hypothermia. The main finding of the current study was that lung protective ventilation had no advantage in preserving the perioperative core temperature compared to conventional ventilation.

Thermoregulation is regulated from the thalamus, and normally, the thermoregulation system activates when the temperature decreases to 0.2°C (1, 13-15). The first 60 min of

heat distribution is the period of thermal redistribution, and the temperature of the patient decreases to 0.5°C - 1.5°C . After 2-4 h of anaesthesia, heat distribution continues with internal redistribution. In the following period, peripheral vasoconstriction develops, and heat loss is compensated (16, 17). Well-known complications of perioperative unintended hypothermia include altered response to hypnotic drugs and neuromuscular blockade, increased intraoperative blood loss and heart problems that affect mortality. Morbidity and mortality increase in relation to these effects (1-3, 18). In the present study, no change was observed in the haemodynamic parameters or blood loss in any patient of both groups.

Current guidelines recommend a tidal volume of 6 mL kg^{-1} for the management of patients with acute lung injury or acute respiratory distress syndrome (19). The application of low-tidal volume in patients undergoing low-risk elective operations is less evident. In addition to the reduction of tidal volume, increasing the level of PEEP is now considered to be an integral part of protective ventilation. Recently, there have been many studies in the literature regarding the effects of PEEP on improving arterial oxygenation or inflammatory response (20, 21). In addition to these benefits, PEEP has positive effects on hypothermia prevention (7).

Peripheral vasoconstriction plays a major role in the thermoregulatory response to reduce body temperature. Therefore, non-thermal factors affecting the cardiovascular system might modulate thermoregulatory control. Cardiopulmonary baroreceptors trigger a reflex that causes vasoconstriction when

the right atrial transmural pressure (RATP) decreases and vasodilation when RATP increases. PEEP, which unloads baroreceptors, attenuates perioperative hypothermia and mediates hypothermia by an increase in the vasoconstriction threshold (22).

Thus far, there have been studies that have compared the effects of different anaesthetic drugs on thermoregulation (23). In a publication comparing total intravenous anaesthesia (TIVA) and sevoflurane anaesthesia, sevoflurane advantage could not be found (12). In addition, Ikeda et al. (14) used propofol anaesthesia in maintenance and compared it with sevoflurane and found no significant results.

Jung et al. (24) compared the effect on thermoregulatory responses according to anaesthetic techniques between inhalation anaesthesia with desflurane and TIVA with propofol and remifentanyl when PEEP was applied in patients undergoing tympanoplasty. It was determined that when PEEP was applied, the peripheral vasoconstriction occurred earlier in the TIVA group, resulting in less heat loss, and it was concluded that anaesthesia with TIVA may be advantageous in core temperature preservation than inhalation anaesthesia (24). PEEP is known to increase the vasoconstriction threshold by baroreceptor unloading. In contrast, in the current study, vasoconstriction threshold levels were not different in the lung protective group; therefore, it was considered that it might have been affected by the use of desflurane as it reduces the vasoconstriction threshold as a nonlinear gradient (24). The PEEP application affected the results positively in the prevention of core temperature and thermoregulatory responses in the studies by An, Sessler and Jung (12, 23, 24). Bime et al. (25) showed the thermoregulatory benefits of PEEP by applying 10 cm H₂O PEEP. Our study has several limitations. First, a 5 cm H₂O PEEP may not be sufficient for baroreceptor unloading in overall and especially in obese patients. Second, the average body mass index (BMI) was 28 kg m⁻². Finally, higher PEEP levels could have been used. However, there were no significant differences in BMI between the groups in the present study.

Conclusion

Lung protective ventilation with low-tidal volume and PEEP application does not protect core temperature compared to conventional mechanical ventilation with high-tidal volume. Lung protective ventilation is currently more commonly used, but the ideal tidal volume or PEEP has not yet been fully elucidated. As a factor, the thermoregulatory responses to these new ventilation strategies may aid in the detection of ideal volumes. Therefore, there is a need for further studies with large patient groups to examine the effects of low-tidal volumes combined with or without PEEP compared to conventional ventilation on thermoregulation.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Afyon Kocatepe University School of Medicine (Date: 11.11.2016, no:58).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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References

1. Sessler DI. Isı Dengesi. In: Miller RD. Miller Anestezi. İzmir: Güven Kitapevi, 2010: 1571-97.
2. Turan İÖ. Termoregülasyon. In: Kecik Y. Temel Anestezi. Ankara: 2012: 359-72.
3. Kayhan Z. Termoregülasyon ve Anestezi Altında Isı Değişiklikleri. In: Kayhan Z. Klinik Anestezi. Ankara: Logos Yayıncılık. 2004: 436-42.
4. Poveda VB, Nascimento AS. The effect of intraoperative hypothermia upon blood transfusion needs and length of stay among gastrointestinal system cancer surgery. *Eur J Cancer Care* 2017; 26: 1-6. [\[CrossRef\]](#)
5. Shaw CA, Steelman VM, DeBerg J, Schweizer ML. Effectiveness of active and passive warming for the prevention of inadvertent hypothermia in patients receiving neuraxial anesthesia: A systematic review and meta-analysis of randomized controlled trials. *J Clin Anesth* 2017; 38: 93-104. [\[CrossRef\]](#)
6. Kuzkov VV, Rodionova LN, Ilyina YY, Ushakov AA, Sokolova MM, Fot EV, et al. Protective ventilation improves gas exchange, reduces incidence of atelectases, and affects metabolic response in major pancreatoduodenal surgery. *Front Med (Lausanne)* 2016; 6: 66-74. [\[CrossRef\]](#)
7. Poole J, McDowell C, Lall R, Perkins G, McAuley D, Gao F, et al. Individual patient data analysis of tidal volumes used in three large randomized control trials involving patients with acute respiratory distress syndrome. *Br J Anaesth* 2017; 118: 570-5. [\[CrossRef\]](#)
8. Sessler D. Temperature monitoring and perioperative thermoregulation. *Anesthesiology* 2008; 109: 318-38. [\[CrossRef\]](#)
9. Mizobe T, Nakajima Y, Sunaguchi M, Ueno H, Sessler DI. Clonidine produces a dose-dependent impairment of baroreflex-mediated thermoregulatory responses to positive end-expiratory pressure in anaesthetized humans. *Br J Anaesth* 2005; 94: 536-41. [\[CrossRef\]](#)

10. Nakajima Y, Mizobe T, Takamata A, Tanaka Y. Baroreflex modulation of peripheral vasoconstriction during progressive hypothermia in anesthetized humans. *Am J Physiol Regul Integr Comp Physiol* 2000; 279: 1430-6. [\[CrossRef\]](#)
 11. Wolthuis EK, Choi G, Delsing MC, Bresser P, Lutter R, Dzoljic M, et al. Mechanical ventilation with lower tidal volumes and positive end-expiratory pressure prevents pulmonary inflammation in patients without preexisting lung injury. *Anesthesiology* 2008; 108: 46-54. [\[CrossRef\]](#)
 12. An TH, Yang JW. Effects of PEEP on the thermoregulatory responses during TIVA in patients undergoing tympanoplasty. *Korean J Anesthesiol* 2011; 61: 302-7. [\[CrossRef\]](#)
 13. Sajid MS, Shakir AJ, Khatri K, Baig MK. The role of perioperative warming in surgery: a systematic review. *Sao Paulo Med J* 2009; 127: 231-7. [\[CrossRef\]](#)
 14. Ikeda T, Sessler DI, Kikura M, Kazama T, Ikeda K, Sato S. Less core hypothermia when anesthesia is induced with inhaled sevoflurane than with intravenous propofol. *Anesth Analg* 1999; 88: 921-4. [\[CrossRef\]](#)
 15. Özer AB, Yıldız AA, Erhan ÖL, Çatak T, Karatepe Ü, Demirel İ, et al. The effect of body mass index on perioperative thermoregulation. *Ther Clin Risk Manag* 2016; 18: 1717-20. [\[CrossRef\]](#)
 16. Sessler DI. Perioperative thermoregulation and heat balance. *Lancet* 2016; 387: 2655-64. [\[CrossRef\]](#)
 17. Dikmen Y. Sıcaklık Monitörizasyonu ve Bozuklukları. In: Duke J. *Anesteziğin Sırları*. Ankara: Nobel Tıp Kitabevi, 2006: 176-81.
 18. Ma H, Lai B, Dong S, Li X, Cui Y, Sun Q, et al. Warming infusion improves perioperative outcomes of elderly patients who underwent bilateral hip replacement. *Medicine (Baltimore)* 2017; 96: e6490. [\[CrossRef\]](#)
 19. Jabaudon M, Godet T, Futier E, Bazin JÉ, Sapin V, Roszyk L, et al. Rationale, study design and analysis plan of the lung imaging morphology for ventilator settings in acute respiratory distress syndrome study (LIVE study): Study protocol for a randomised controlled trial. *Anaesth Crit Care Pain Med* 2017; 36: 301-6. [\[CrossRef\]](#)
 20. Kim JY, Shin CS, Kim HS, Jung WS, Kwak HJ. Positive end-expiratory pressure in pressure-controlled ventilation improves ventilatory and oxygenation parameters during laparoscopic cholecystectomy. *Surg Endosc* 2010; 24: 1099-103. [\[CrossRef\]](#)
 21. Talab HF, Zabani IA, Abdelrahman HS, Bukhari WL, Mamoun I, Ashour MA, et al. Intraoperative ventilatory strategies for prevention of pulmonary atelectasis in obese patients undergoing laparoscopic bariatric surgery. *Anesth Analg* 2009; 109: 1511-6. [\[CrossRef\]](#)
 22. Nakajima Y, Mizobe T, Takamata A, Tanaka Y. Baroreflex modulation of peripheral vasoconstriction during progressive hypothermia in anesthetized humans. *Am J Physiol Regulatory Integrative Comp Physiol* 2000; 279: 1430-6. [\[CrossRef\]](#)
 23. Sessler DI. The thermoregulation story. *Anesthesiology* 2013; 118: 181-6. [\[CrossRef\]](#)
 24. Jung KT, Kim SH, Lee HY, Jung JD, Yu BS, Lim KJ, et al. Effect on thermoregulatory responses in patients undergoing a tympanoplasty in accordance to the anesthetic techniques during PEEP: A comparison between inhalation anesthesia with desflurane and TIVA. *Korean J Anesthesiol* 2014; 67: 32-7. [\[CrossRef\]](#)
 25. Bime C, Fiero M, Lu Z, Oren E, Berry CE, Parthasarathy S, et al. High Positive End-Expiratory Pressure Is Associated with Improved Survival in Obese Patients with Acute Respiratory Distress Syndrome. *Am J Med* 2017; 130: 207-13. [\[CrossRef\]](#)
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