Zero-Heat-Flux Thermometry for Non-Invasive Measurement of Core Body Temperature in Pigs

Maria Guschlbauer, Alexandra C. Maul, Xiaowei Yan, Holger Herff, Thorsten Annecke, Anja Sterner-Kock, Bernd W. Böttiger, Daniel C. Schroeder

1 Center for Experimental Medicine, University Hospital of Cologne, Cologne, Germany, 2 Department of Anaesthesiology and Intensive Care Medicine, University Hospital of Cologne, Cologne, Germany

Abstract

Hypothermia is a severe, unpleasant side effect during general anesthesia. Thus, temperature surveillance is a prerequisite in general anesthesia settings during experimental surgeries. The gold standard to measure the core body temperature (Tcore) is placement of a Swan-Ganz catheter in the pulmonary artery, which is a highly invasive procedure. Therefore, Tcore is commonly examined in the urine bladder and rectum. However, these procedures are known for their inaccuracy and delayed record of temperatures. Zero-heat-flux (ZHF) thermometry is an alternative, non-invasive method quantifying Tcore in human patients by applying a thermosensoric patch to the lateral forehead. Since the porcine cranial anatomy is different to the human’s, the optimal location of the patch remains unclear to date. The aim was to compare three different patch locations of ZHF thermometry in a porcine hypothermia model. Hypothermia (33.0°C Tcore) was conducted in 11 anesthetized female pigs (26-30kg). Tcore was measured continuously by an invasive Swan-Ganz catheter in the pulmonary artery (Tpulm). A ZHF thermometry device was mounted on three different defined locations. The smallest average difference between Tpulm and TZHF during stable temperatures was 0.21 ± 0.16°C at location A, where the patch was placed directly behind the eye. Also during rapidly changing temperatures location A showed the smallest bias with 0.48 ± 0.29°C. Location A provided the most reliable data for Tcore. Therefore, the ZHF thermometry patch should be placed directly behind the left temporal corner of the eye to provide a non-invasive method for accurate measurement of Tcore in pigs.

Introduction

Pigs are commonly used as experimental animal models to mirror human conditions. They often undergo general anesthesia and are prone to develop a hypothermic status, known as perioperative hypothermia. Anesthesia-induced impairment of thermoregulatory control, redistribution of core body heat to the periphery and reduction of metabolic energy production are considered to be responsible for perioperative hypothermia.
[11–14]. Various consequences such as coagulopathy [7, 15–17], imbalances in the electrolyte metabolism, increased hematocrit, tubular necrosis, shivering [18–21] as well as higher incidence of wound infections and healing have been described [7, 22–24]. To avoid the impact of perioperative hypothermia on experimental data, accurate measurement of core body temperature (Tcore) is a prerequisite during general anesthesia [7, 11, 25–29]. The gold standard to record Tcore is to measure the blood temperature in the pulmonary artery (Tpulm) using a Swan-Ganz catheter [6, 28, 30–32]. However, placement of a Swan-Ganz catheter is highly invasive and thus not always suitable in porcine experimental settings.

Peripheral measurement sites, such as the temperatures in urinary bladder and rectum, are commonly used to continuously monitor Tcore. Albeit, peripheral temperature measurement sites show a time delay compared to pulmonary artery temperature during rapidly changing temperatures resulting in a misinterpretation of Tcore [33–36].

In human medicine a non-invasive method to accurately evaluate core body temperature is the Zero-heat-flux (ZHF) technology, first described in 1973 [37]. An insulator patch applied to the lateral forehead and covered by an electric heater is used to stop surface convection, creating an isothermic tunnel from the core body to the skin surface. As soon as heater- and skin-temperatures are equal, the subdermal temperature can be measured approximately 1 to 2 cm below the skin surface. In well-perfused parts of the body, tissue temperature below the skin surface approximates core body temperature [7, 26, 29, 37, 38].

To date, ZHF technology has not been evaluated in pigs. As the porcine cranial anatomy differs from the human structures, the appropriate patch location on the porcine head is unknown. The aim of the present study was to compare three different ZHF patch locations on the porcine forehead to evaluate whether ZHF technology is feasible in pigs. Therefore, the ZHF device was tested during an experimentally induced porcine model of mild therapeutic hypothermia. It was hypothesized that in pigs the ZHF device, placed on a defined location at the forehead, serves as a reliable non-invasive method to evaluate Tcore corresponding to pulmonary artery temperature.

**Material and Methods**

**Animals**

11 female crossbred growing pigs (Landrace x Pietrain) weighing 29.1 ± 1.4 kg underwent a hypothermia protocol under general anesthesia. All experimental procedures were ethically approved by the governmental authority responsible for animal welfare in the state of North Rhine-Westphalia (Landesamt für Natur, Umwelt und Verbraucherschutz Nordrhein-Westfalen, Germany). All procedures were in accordance with the German Laws for Animal Protection. Animal care and use was performed by qualified staff members, supervised by a veterinarian, and all facilities and transportation procedures comply with current legal requirements. Pigs were purchased from a local breeding farm (Kalkar, Germany). Animals were allowed to acclimatize for at least 10 days before interventions started. The pigs were group housed in straw bedded 9.3 m² boxes (groups of 2 to 5 animals) in the Centre for Experimental Medicine at the University Hospital of Cologne. They were fed a standard diet (900 g/animal/day, Universal Mast, RWZ, Cologne, Germany) and had free access to water. To satisfy exploring behavior, enrichment was provided and hay was offered daily. Photoperiods were 12:12 hours light:dark and ambient temperature was maintained at 20±1°C. At the end of the intervention pigs were euthanized using an overdose of pentobarbital-sodium (80mg/kg; Euthadorm, CP Pharma, Burgdorf, Germany) injected intravenously during deep anesthesia.
Anesthesia and analgesia

Pigs were fasted for 12 hours prior to the start of the interventions while water was always accessible. Before induction of anesthesia, the animals were separated from the group, with remaining visual contact. The pigs received an intramuscular injection of azaparone (2 mg/kg body weight; Stresnil, Janssen, Neuss, Germany), ketamine (20 mg/kg body weight; Ketavet 100, Pfizer, Berlin, Germany) and atropine (0.02 mg/kg body weight, Atropin, Braun, Melsungen, Germany) for premedication. During transport to the intervention room, oxygen was administered via face mask. Pigs were bedded in a supine position. By use of a 20 gauge catheter (Vasovet, Braun Melsungen, Melsungen, Germany) in the lateral auricular vein, a bolus of propofol (Propofol 2% MCT, Fresenius, Bad Homburg, Germany) was administered prior to endotracheal intubation using an endotracheal tube (6–6.5 ID mm, Teleflex Medical, Kernen, Germany). Ventilation was performed using a volume-controlled ventilator setting (Fabius GS, Dräger, Lübeck, Germany) of 8 ml per kilogram bodyweight tidal volume to obtain normocapnia with a PaCO$_2$ of 35 mmHg to 45 mmHg, a FIO$_2$ = 0.25 and a positive end-expiratory pressure of 5 mmHg. Total intravenous anesthesia (TIVA) using a combination of propofol (5–7 mg/kg/h i.v.), midazolam (1.2 mg/kg/h i.v.; Midazolam, Rotexmedica, Trittau, Germany) and fentanyl (12–15 μg/kg/h i.v.; Fentanyl, Rotexmedica, Trittau, Germany) was applied to maintain anesthesia. Fluid management was performed using 37°C preheated Ringer’s solution (Ringerlösung Fresenius, Fresenius Kabi, Bad Homburg, Germany) 7 to 10 ml/kg per hour, dependent on the circulatory situation. A standard lead II electrocardiogram was used to monitor cardiac rhythm (Philips Medizinsysteme, Böblingen, Germany).

Preparation, catheters and temperature measurement

When the state of surgical tolerance was reached, a 14 gauge saline-filled catheter (Arrow International, Reading, USA) was inserted into the right Vena femoralis for TIVA and fluid administration. The right Arteria femoralis was catheterized (Arterial leadercath, Vygon, Ecouen, France) to record arterial blood pressure using a transducer that was aligned at the level of the right atrium (Philips M1097A, Philips Medizinsysteme, Böblingen, Germany). A Swan-Ganz catheter (5 French, Arrow International, Reading, USA) was inserted via the right internal jugular vein into the pulmonary artery in order to measure pulmonary artery temperature. A urine catheter (12 Ch, Balloon Catheter, Teleflex Medical, Kernen, Germany) was placed in the bladder via median laparotomy. Spontaneous cooling of the pigs before starting the experiment was prevented by covering the animals with heating-blankets (Bairhugger, 3M, Neuss, Germany). A 3M SpotOn patch (3MTM SpotOnTM, 3M, Neuss, Germany) was stuck to the shaved skin on three different, defined localizations (Fig 1): A: directly behind the left temporal corner of the eye (4 pigs), B: obliquely above the eye on the forehead, this position is equivalent to human application of 3M SpotOn (3 pigs), C: central on the forehead (4 pigs).

Thereafter the Zero-heat-flux temperature (T$_{ZHF}$) device was connected to the patches to record temperature. A cooling system (Variotherm 555, Hirtz & coKG, Cologne, Germany) was applied intraoesophageally. Mild therapeutic hypothermia (33°C) was conducted by an automatic feedback cooling system. The cooling device continuously registered T$_{pulm}$ and automatically adjusted the cooling-temperature to the pre-settings of the study protocol.

Experimental Design

Pigs were cooled from $T_{pulm} = 37.7 \pm 0.6^\circ C$ to 33°C as fast as possible (= cooling phase). Thereafter, $T_{pulm}$ was kept at 33°C (= maintaining phase) for 1 hour. During this process $T_{ZHF}$ and $T_{pulm}$ were recorded every 5 minutes to determine the precision of the ZHF device in measuring core body temperature compared to $T_{pulm}$. Altogether the study included 363 paired
temperature measurements of $T_{ZHF}$ and $T_{pulm}$ that were used for statistical analysis. $n = 130$ paired measurements were recorded at ZHF location A in four pigs, thereof $n = 78$ paired measurements during the cooling phase and $n = 52$ during the maintaining phase. At ZHF location B altogether $n = 98$ paired measurements were recorded in three pigs, thereof $n = 59$ during the cooling phase and $n = 39$ during the maintaining phase. At ZHF location C in total $n = 135$ paired measurements were recorded in four pigs, thereof $n = 83$ were measured during the cooling phase and $n = 52$ during the maintaining phase. The differences in the number of paired measurements per animal in the cooling phase resulted from the different durations of this specific phase.

Statistics

Statistical analysis was performed using the Bland-Altman plot [39, 40] to calculate the bias and 95% limit of agreement (GraphPad Prism Version 6.0, GraphPad Software, La Jolla, California). Each dot in the Bland Altman plot represents the results of one temperature pair of $T_{pulm}$ and $T_{ZHF}$ in one animal at time $t$. The paired Student’s t-tests were performed with Stata (Stata 13.1, DatacorpLP, College Station, USA). Values are expressed as mean ± SD. P values less than 0.05 were set as significant. Starting point of the maintaining phase was defined as the time when the difference between two following $T_{ZHF}$ values was zero. The bias of $T_{ZHF}$ compared to $T_{pulm}$ in the cooling phase was statistically decomposed into two factors: a level effect caused by the intrinsic ZHF device bias and a time effect that caused the delay of $T_{ZHF}$ during the rapidly changing temperatures in the cooling phase.

Results

Mean cooling rate was $2.8 ± 0.46°C/h$. Goal temperature of $T_{pulm} = 33°C$ was attained after $100 ± 17$ minutes. An overview of the temperature patterns are given in Fig 2.
Tpulm differs significantly from TZHF at all three locations during cooling and maintaining phase (p < 0.001). Results of Bland Altman plots for cooling and maintaining phase are shown in Fig 3 and Table 1.

As the bias during the cooling phase was significantly higher compared to the maintaining phase at all three locations (A, B, C) (Table 1), the bias was statistically split into two effects: a level effect, caused by the ZHF device that exists in both phases, and a time effect, present only during rapidly changing temperatures in the cooling phase. **Level effect:** both temperature measuring methods revealed constant temperatures during the maintaining phase (Fig 2). Therefore, the bias during the maintaining phase was equalized as the intrinsic level effect of the ZHF device. Results are shown in Table 1. **Time effect:** TZHF values of the cooling phase were adjusted for the level effect (= TZHF-adj) to quantify the time effect on the bias in the cooling phase. Data are shown in Table 1. The delay-duration of TZHF compared to Tpulm was calculated by comparing Tpulm temperatures (at timepoint t0) with TZHF-adj temperatures, which were both recorded at time points 5 (t0+5), 10 (t0+10) and 15 (t0+15) minutes after t0 (Table 2).

TZHF-A showed a time delay between 5 and 10 minutes compared to Tpulm. At location B the time delay was exactly 10 minutes because TZHF-adj-B at t0+10 did not significantly differ from Tpulm at t0 (p > 0.05). TZHF-adj-C at t0+10 is significantly lower than Tpulm at t0 (p < 0.05) indicating a time delay between 5 and 10 minutes.

**Discussion**

In the present study it could be demonstrated for the first time that Zero-heat-flux technology for temperature measurement is applicable in pigs. Three different locations to place thermosensoric patches for the non-invasive Zero-heat-flux temperature measurement were compared, using pulmonary artery temperature for comparison.

Accurate management of core body temperature in surgical settings under general anesthesia is indispensable in humans as well as in pigs in order to prevent perioperative hypothermia. Furthermore, in experimental settings, where normothermia is desirable, identification of a rapidly changing Tcore is necessary in order to prevent perioperative hypothermia or malignant hyperthermia. Hence, reliable methods for temperature surveillance are a prerequisite for different surgical interrogations in the pig [3, 25, 28, 36, 41].

Common, non-invasive methods to measure core body temperature in pigs during anesthesia are placement of a thermosensoric rectal probe or a urinary bladder catheter for temperature measurement. Those peripheral sites do not reliably display fast changes of the core body temperature in humans and pigs. Literature revealed that both, urinary and rectal temperature, showed bias values >0.5°C compared to Tcore. Additionally, urinary bladder temperature may be misinterpreted due to decreased urine production [25, 26, 30, 32–34, 36]. Musk et al. (2015) compared porcine rectal to oesophageal temperatures during small surgery procedures. They showed a bias of 0.69°C, with 95% limits of agreement of -1.18 to 2.57°C taken from Bland-Altman analysis. The high bias and the wide range of the limits of agreement imply that rectal temperature is unsuitable for measuring core body temperature [34].

The ZHF device in human application accomplished a bias of -0.23°C with 95% limits of agreement of -1.05 and +0.59°C, compared to pulmonary artery temperature [29]. In accordance to the results of Eshraghi et al. (2014), in the present study the porcine application of the
Fig 3. Bland Altman plots comparing $T_{\text{pulm}}$ and $T_{\text{ZHF}}$ for ZHF location A (4 pigs), B (3 pigs) and C (4 pigs) during cooling and maintaining phase.

$T_{\text{pulm}} =$ blood temperature in the pulmonary artery, $T_{\text{ZHF}} =$ temperature measured by the ZHF device.

doi:10.1371/journal.pone.0150759.g003
The ZHF device at location A showed a bias of 0.21 ± 0.16°C in the maintaining phase. Both locations, B and C, revealed a significantly higher bias than location A (Table 1). Nevertheless, considering a maximal accepted difference between two comparable temperature measuring methods of 0.5°C [11, 29, 42] all ZHF locations show a clinically acceptable bias in the maintaining phase (Table 1). In summary, the ZHF device at location A is applicable for a reliable measurement of constant Tcore in pigs. During the cooling phase the bias was significantly higher than in the maintaining phase at all three locations (A, B, C) (p < 0.001, Table 1). Thus, an influence of fast changing temperatures on the reliability of TZHF was supposed. Similar phenomena have already been described before [1, 33, 36]. In a study of Krizanac et al. (2010) temperatures measured by tracheal temperature probes were compared to the pulmonary artery temperature. Fast cooling resulted in a significantly higher bias than slow cooling, implicating a delay of tracheal compared to pulmonary artery temperature during rapidly changing temperatures [1]. During the cooling phase, the time effect was quantified (Table 1) and the delay of TZHF compared to Tpulm was evaluated as 5 to 10 minutes for location A and C and exactly 10 minutes for location B. Bias during cooling at location A was 0.48 ± 0.29°C. Though a time delay of 5 to 10 minutes was present during forced cooling, the deviation of TZHF compared to Tpulm was in compliance with the clinically acceptable bias range of < 0.5°C [11, 29, 42]. Both, location B and C, included significantly higher bias values for the cooling phase than location A (Table 1), and were therefore assessed as not convenient locations to monitor a precise temperature course compared to location A.

The setting of mild therapeutic hypothermia was chosen to examine the reliable functionality of the ZHF device during rapidly decreasing and constant temperatures. After the cooling

### Table 1. Bias of TZHF and Tpulm for each ZHF location (A, B, C) in cooling phase, maintaining phase and the time effect.

|       | cooling phase | maintaining phase ( ≠ level effect) | time effect during cooling phase ( = bias of cooling phase – level effect) |
|-------|---------------|-------------------------------------|--------------------------------------------------------------------------------|
| bias-A| 0.48 ± 0.29   | 0.21 ± 0.16§                        | 0.27 ± 0.28                                                                      |
| bias-B| 0.75 ± 0.33***| 0.36 ± 0.12***§                     |                                                                                |
| bias-C| 0.80 ± 0.27***| 0.41 ± 0.16***§                     | 0.39 ± 0.33*                                                                    |

Bias = mean difference between TZHF and Tpulm. Data are shown as mean difference ± SD (°C)

*** = significantly different to bias-A (p<0.001)

** = significantly different to bias-A (p<0.05)

§ = significantly different to the bias in the corresponding cooling phase (p<0.001)

doi:10.1371/journal.pone.0150759.t001

### Table 2. Time delay of TZHF compared to Tpulm during the cooling phase.

|       | Tpulm at t₀ & TZHFA-adj at t₀+5 | Tpulm at t₀ & TZHFA-adj at t₀+10 | Tpulm at t₀ & TZHFA-adj at t₀+15 |
|-------|----------------------------------|-----------------------------------|----------------------------------|
| bias-A| 0.08±0.23**                      | -0.11±0.18§                      | -0.30±0.17§                     |
| bias-B| 0.17±0.29***                     | -0.05±0.27                       | -0.26±0.26§                     |
| bias-C| 0.16±0.26***                     | -0.07±0.27§                      | -0.28±0.30§                     |

Bias was calculated comparing Tpulm at t₀ and TZHFA-adj at 5, 10 and 15 minutes after t₀ (t₀+5, t₀+10, t₀+15) for ZHF location A, B and C. Data are shown as mean difference ± SD (°C), bias = mean difference between TZHFA-adj and Tpulm

*** = TZHFA-adj is significantly higher than Tpulm (p<0.01)

** = TZHFA-adj is significantly higher than Tpulm (p<0.001)

§ = TZHFA-adj is significantly lower than Tpulm (p<0.001)

# = TZHFA-adj is significantly lower than Tpulm (p<0.05)

doi:10.1371/journal.pone.0150759.t002
phase, temperature was constantly maintained at 33°C, which is far below the physiological core body temperature of pigs during general anesthesia. At 33°C the ZHF device reliably displayed core body temperature. Therefore, it was extrapolated that the device is able to display a precise temperature monitoring also in constant physiological ranges, which has to be proven in further studies.

To conclude, the ZHF device placed at location A, directly behind the lateral eye angle, provides the most accurate display of core body temperature in pigs. Thus, under clinical aspects, the device is judged as applicable as a non-invasive method for porcine $T_{\text{core}}$ measurement in experimental settings under general anesthesia.

Acknowledgments

The Authors are thankful to Dr. Rafael Gralla for statistical support and Laura Webb for proof-reading the manuscript.

Author Contributions

Conceived and designed the experiments: DCS HH MG ACM. Performed the experiments: MG ACM DCS XY. Analyzed the data: ACM. Contributed reagents/materials/analysis tools: TA BWB HH ASK. Wrote the paper: ACM MG DCS.

References

1. Krizanac D, Haugk M, Sterz F, Weihs W, Holzer M, Bayegan K, et al. Tracheal temperature for monitoring body temperature during mild hypothermia in pigs. Resuscitation. 2010; 81(1):87–92. Epub 2009/11/21. doi: 10.1016/j.resuscitation.2009.10.006 PMID: 19926384.

2. Wittwer T, Rahmanian P, Choi YH, Zeriouh M, Karavidis S, Neel K, et al. Mesenchymal stem cell pre-treatment of non-heart-beating-donors in experimental lung transplantation. J Cardiothorac Surg. 2014;9:151. Epub 2014/09/03. doi: 10.1186/s13019-014-0151-3 PMID: 25179441; PubMed Central PMCID: PMCPmc4169637.

3. Pehbock D, Dietrich H, Klima G, Paal P, Lindner KH, Wenzel V. Anesthesia in swine: optimizing a laboratory model to optimize translational research. Der Anaesthesist. 2015; 64(1):65–70. Epub 2014/11/12. doi: 10.1007/s00101-014-2371-2 PMID: 25384955.

4. Swindle MM, Makin A, Herron AJ, Clubb FJ Jr., Frazier KS. Swine as models in biomedical research and toxicology testing. Vet Pathol. 2012; 49(2):344–56. Epub 2011/03/29. doi: 10.1177/0300985811402846 PMID: 21441112.

5. Smith AC, Swindle MM. Preparation of swine for the laboratory. ILAR journal / National Research Council, Institute of Laboratory Animal Resources. 2006; 47(4):358–63. PMID: 16963815.

6. Torossian A, Brauer A, Hooker J, Bein B, Wulf H, Horn EP. Preventing inadvertent perioperative hypothermia. Deutsches Arzteblatt international. 2015; 112(10):166–72. Epub 2015/04/04. doi: 10.3238/arztebl.2015.0166 PMID: 25937741; PubMed Central PMCID: PMCPmc4383851.

7. Iden T, Horn EP, Bein B, Bohm R, Beece J, Hooker J. Intraoperative temperature monitoring with zero heat flux technology (3M SpotOn sensor) in comparison with sublingual and nasopharyngeal temperature: An observational study. Europ J Anaesthesiol. 2015. Epub 2015/02/19. doi: 10.1097/aja.0000000000000222 PMID: 25693138.

8. Sterz F, Behringer W, Holzer M. Global hypothermia for neuroprotection after cardiac arrest. Acute Cardiac Care. 2006; 8(1):25–30. Epub 2006/05/25. doi: 10.1080/14628640600621371 PMID: 16720424.

9. Kulstad EB, Naiman M, Shanley P, Garrett F, Haryu T, Waller D, et al. Temperature modulation with an esophageal heat transfer device—a pediatric swine model study. BMC Anesthesiol. 2015; 15:16. Epub 2015/02/17. doi: 10.1186/1471-2253-15-16 PMID: 25685058; PubMed Central PMCID: PMCPmc4327961.

10. Swindle M. Swine in the Laboratory: Surgery, Anesthesia, Imaging, and Experimental Techniques, Second Edition: CRC Press; 2007.

11. Sessler DI. Temperature monitoring and perioperative thermoregulation. Anesthesiol. 2008; 109(2):318–38. Epub 2008/07/24. doi: 10.1097/ALN.0b013e31817f6d76 PMID: 18648241; PubMed Central PMCID: PMCPmc2614355.
12. Inderbitzen B, Yon S, Lasheras J, Dobak J, Perl J, Steinberg GK. Safety and performance of a novel intravascular catheter for induction and reversal of hypothermia in a porcine model. Neurosurg. 2002; 50(2):364–70. Epub 2002/02/15. PMID: 11844272.

13. Beck E, Langer M, Mauro PD, Prato P. Efficacy of intraoperative heat administration by ventilation with warm humidified gases and an oesophageal warming system. BJA Anaesth. 1996; 77(4):530–3. Epub 1996/10/01. PMID: 8943342.

14. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, et al. Heat flow and distribution during induction of general anesthesia. Anesthesiol. 1995; 82(3):662–73. Epub 1995/03/01. PMID: 7879935.

15. Rohrer MJ, Natale AM. Effect of hypothermia on the coagulation cascade. Crit Care Med. 1992; 20(10):1402–5. Epub 1992/10/01. PMID: 1395660.

16. Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative hypothermia on blood loss and transfusion requirement. Anesthesiol. 2008; 108(1):71–7. Epub 2007/12/25. doi: 10.1097/01.anes.0000296719.73450.52 PMID: 18156884.

17. Gong P, Zhang MY, Zhao H, Tang ZR, Hua R, Mei X, et al. Effect of mild hypothermia on the coagulation-fibrinolysis system and physiological anticoagulants after cardiopulmonary resuscitation in a porcine model. PloS one. 2013; 8(6):e67476. Epub 2013/07/03. doi:10.1371/journal.pone.0067476 PMID: 23818980; PubMed Central PMCID: PMCPmc3688589.

18. Kerenyi A, Kelen D, Faulkner SD, Bainbridge A, Chandrasekaran M, Cady EB, et al. Systemic effects of whole-body cooling to 35 degrees C, 33.5 degrees C, and 30 degrees C in a piglet model of perinatal asphyxia: implications for therapeutic hypothermia. Pediat Res. 2012; 71(5):573–82. doi:10.1038/pr.2012.8 PMID: 22314664; PubMed Central PMCID: PMC4241373.

19. Wladis A, Hahn RG, Hjelmqvist H, Brismar B, Kjellstrom BT. Acute hemodynamic effects of induced hypothermia in hemorrhagic shock: an experimental study in the pig. Shock. 2001; 15(1):60–82. Epub 1998/09/25. doi:10.1097/00006736-199809250-00002 PMID: 9751545.

20. Wladis A, Hjelmqvist H, Brismar B, Kjellstrom BT. Acute metabolic and endocrine effects of induced hypothermia in hemorrhagic shock: an experimental study in the pig. J Trauma. 1998; 45(3):527–33. Epub 2001/02/24. PMID: 1198359.

21. Martini WZ, Pusateri AE, Usclowitz JM, Delgado AV, Holcomb JB. Independent contributions of hypothermia and acidosis to coagulopathy in swine. J Trauma. 2005; 58(5):1002–9; discussion 9–10. Epub 2005/05/28. PMID: 15920416.

22. Kurz A, Sessler DI, Lenhardt R. Perioperative normothermia to reduce the incidence of surgical-wound infection and shorten hospitalization. Study of Wound Infection and Temperature Group. N Engl J Med. 1996; 334(19):1209–15. Epub 1996/05/09. doi: 10.1056/nejm199605093341901 PMID: 8606715.

23. Sessler DI. Mild perioperative hypothermia. N Engl J Med. 1997; 336(24):1730–7. Epub 1997/06/12. doi: 10.1056/nejm199706123362407 PMID: 9180091.

24. Melling AC, Ali B, Scott EM, Leaper DJ. Effects of preoperative warming on the incidence of wound infection after clean surgery: a randomised controlled trial. Lancet. 2001; 358(9285):876–80. Epub 2001/09/25. doi:10.1016/s0140-6736(01)06071-8 PMID: 11567703.

25. Hanneman SK, Jesurum-Urbaitis JT, Bickel DR. Comparison of methods of temperature measurement in swine. Lab Anim. 2004; 38(3):297–306. Epub 2004/06/23. doi: 10.3201/eid0905.020556 PMID: 15207041.

26. Kaiser GM, Heuer MM, Fruhauf NR, Kuhne CA, Broelsch CE. General handling and anesthesia for experimental surgery in pigs. JSurg Res. 2006; 130(1):73–9. Epub 2005/11/18. doi:10.1016/j.jss.2005.07.012 PMID: 16289594.

27. Krizanac D, Stratil P, Hoerburger D, Testori C, Wallmueller C, Schober A, et al. Femoro-iliacal artery versus pulmonary artery core temperature measurement during therapeutic hypothermia: an observational study. Resuscitation. 2013; 84(6):805–9. Epub 2012/12/04. doi:10.1016/j.resuscitation.2012.11.022 PMID: 23200998.

28. Eshraghi Y, Nasr V, Parra-Sanchez I, Van Duren A, Botham M, Santoscoy T, et al. An evaluation of a zero-heat-flux cutaneous thermometer in cardiac surgical patients. Anesth Analg. 2014; 119(3):543–9. Epub 2014/07/22. doi: 10.1213/ane.0000000000000319 PMID: 25045862.

29. Polderman KH, Herold I. Therapeutic hypothermia and controlled normothermia in the intensive care unit: practical considerations, side effects, and cooling methods. Crit Care Med. 2009; 37(3):1101–20. Epub 2009/02/25. doi: 10.1097/CCM.0b013e3181962ad5 PMID: 19237924.
31. Robinson JL, Seal RF, Spady DW, Joffres MR. Comparison of esophageal, rectal, axillary, bladder, tympanic, and pulmonary artery temperatures in children. J Pediatr. 1998; 133(4):553–6. Epub 1998/10/27. PMID: 9787697.

32. Imrie MM, Hall GM. Body temperature and anaesthesia. BJ Anaesth. 1990; 64(3):346–54. Epub 1990/03/01. PMID: 2183863.

33. Stone JG, Young WL, Smith CR, Solomon RA, Wald A, Ostapkovich N, et al. Do standard monitoring sites reflect true brain temperature when profound hypothermia is rapidly induced and reversed? Anesthesiology. 1995; 82(2):344–51. Epub 1995/02/01. PMID: 7856892.

34. Musk GC, Costa RS, Tuke J. Body temperature measurements in pigs during general anaesthesia. Lab Anim. 2015. Epub 2015/06/03. doi: 10.1177/0023677215590301 PMID: 26033873.

35. Weingart S, Mayer S, Polderman K. Rectal probe temperature lag during rapid saline induction of hypothermia after resuscitation from cardiac arrest. Resuscitation. 2009; 80(7):837–8. Epub 2009/05/27. doi: 10.1016/j.resuscitation.2009.04.017 PMID: 19467758.

36. Shin J, Kim J, Song K, Kwak Y. Core temperature measurement in therapeutic hypothermia according to different phases: comparison of bladder, rectal, and tympanic versus pulmonary artery methods. Resuscitation. 2013; 84(6):810–7. Epub 2013/01/12. doi: 10.1016/j.resuscitation.2012.12.023 PMID: 23306812.

37. Fox RH, Solman AJ, Isaacs R, Fry AJ, MacDonald IC. A new method for monitoring deep body temperature from the skin surface. Clin Sci. 1973; 44(1):81–6. Epub 1973/01/01. PMID: 4684307.

38. Brajkovic D, Ducharme MB. Confounding factors in the use of the zero-heat-flow method for non-invasive muscle temperature measurement. Eur J Appl Physiol. 2005; 94(4):386–91. Epub 2005/05/03. doi: 10.1007/s00421-005-1336-1 PMID: 15864635.

39. Altman DG, Bland JM. Measurement in Medicine: The Analysis of Method Comparison Studies. J Roy Stat Soc Ser D (The Statistician). 1983; 32(3):307–17. 10.2307/2987937.

40. Giavarina D. Understanding Bland Altman analysis. Biochem Med. 2015; 25(2):141–51. Epub 2015/06/26. doi: 10.11613/bm.2015.015 PMID: 26110027; PubMed Central PMCID: PMCPmc4470095.

41. Polderman KH, Varon J. How low should we go? Hypothermia or strict normothermia after cardiac arrest? Circulation. 2015; 131(7):669–75. Epub 2015/02/19. doi: 10.1161/circulationaha.114.012165 PMID: 25691702.

42. Winkler M, Akca O, Birkenberg B, Hetz H, Scheck T, Arkilic CF, et al. Aggressive warming reduces blood loss during hip arthroplasty. Anesth Analges. 2000; 91(4):978–84. Epub 2000/09/27. PMID: 11004060.