Induction techniques that reduce redistribution hypothermia: A prospective, randomized, controlled, single blind effectiveness study.

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Abstract

BACKGROUND While much effort has been devoted to correcting intraoperative hypothermia, less attention has been directed to preventing redistribution hypothermia. In this study, we compared three different anesthetic induction techniques to standard IV propofol inductions (control) in their effect on reducing redistribution hypothermia.

METHODS Elective, afebrile patients, age 18 to 55 years, were randomly assigned to one of four groups (n=50 each). Group “INH/100” was induced with 8% sevoflurane in 100% oxygen, Group “INH/50” with 8% sevoflurane in 50% oxygen and 50% nitrous oxide, Group “PROP” with 2.2 mg/kg propofol, and Group “Phnl/PROP” with 2.2 mg/kg propofol immediately preceded by 160 mcg phenylephrine. Patients were maintained with sevoflurane in 50% nitrous oxide and 50% oxygen in addition to opioid narcotic. Forced air warming was used. Core temperatures were recorded every 15 minutes after induction for one hour. RESULTS Compared to control group PROP, the mean temperatures in groups INH/100, INH/50, and Phnl/PROP were higher 15, 30, 45 and 60 minutes after induction (p<0.006 for all comparisons), averaging between 0.39 o C and 0.54 o C higher. In group PROP, 60% of patients had at least one temperature below 36.0 o C in the first hour whereas only 16% did in each of groups INH/100, INH/50, and Phnl/PROP (p<0.0001 in each group compared to PROP). CONCLUSIONS In this effectiveness trial, inhalation inductions with sevoflurane or with prophylactic phenylephrine bolus prior to propofol induction reduced the magnitude of redistribution hypothermia by an average of 0.4 to 0.5°C in patients aged 18 to 55 years.

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Background

Hypothermia has multiple adverse consequences and should be avoided.1,2 In studies
assessing whether patients were hypothermic, typically the end of case temperature has
been used for this determination and its association with complications. However, there is
increasing recognition that intraoperative temperature matters.
Anesthesia induction with propofol is known to cause a rapid and clinically important
temperature decrease due to redistribution hypothermia, typically by about 1.5°C.³ Ikeda et al showed there is on average 0.7°C less redistribution hypothermia when patients are
induced with an inhalation induction rather than with intravenous propofol.³ However, the
use of inhalation inductions has not been widely adapted. Sun et al documented that
hypothermia is routine during the first hour of anesthesia.⁴ While there is great effort
expended to warm patients intraoperatively, relatively little attention has been directed to
preventing redistribution hypothermia. Some hypothermia complications occur intra-
operatively (e.g., coagulopathy, increased transfusion requirements), some post-
operatively (e.g., shivering, delayed emergence) and some likely both (e.g., infection
risk).⁴-⁶ The contribution of intraoperative hypothermia to postoperative complications
often may be unrecognized. End of case hypothermia indicates intraoperative
hypothermia. End of case normothermia does not imply intraoperative normothermia. A
patient may have been hypothermic intraoperatively, having suffered the consequences of
intraoperative hypothermia, achieving normothermia only at the end of the case. It is
plausible that if redistribution hypothermia can be reduced, one may be able to reduce the
intraoperative and postoperative complications associated with hypothermia.
Vasodilation causes redistribution hypothermia by increasing blood flow to the cooler
peripheral and dermal thermal compartments resulting in heat transfer away from the
warmer core. Our research hypothesis was that inductions that cause less vasodilation
than propofol alone inductions will result in less redistribution hypothermia. The purpose
of this effectiveness study is to compare the effect of three such alternative induction techniques to standard propofol inductions on core temperature during the first hour of anesthesia.

Methods

This study and consent forms were approved by our IRB and submitted to clinical-trials.gov as NCT02331108 by Jonathan V. Roth on November 20, 2014. Informed consent was obtained from all participating patients. The manuscript complies with the CONSORT requirements. This study was performed at the Albert Einstein Healthcare Network in Philadelphia, Pennsylvania during 2014 and 2015.

The four groups of 50 patients each are described in Table 1. Inclusion and exclusion criteria are presented in Table 2. After enrollment, random assignments were contained in opaque envelopes that were opened immediately before induction of anesthesia. Each of the envelopes contained one of the four group designations, 50 envelopes for each group. Randomization was achieved by putting the envelopes in a basket and mechanically mixing the envelopes within the basket. When a patient was entered into the study, an opaque envelope was selected arbitrarily from any location in the stack.

For all patients, operating rooms were kept between 21°C and 24°C with a target of 22°C. No patients were prewarmed. Upon entering the operating room, cotton blankets were placed on all patients covering their lower extremities, abdomen, and thorax. These blankets were removed after induction to allow for forced air warming (FAW) blanket placement and surgical positioning, preparation, and draping. All operating rooms had the same air flow design. Patients were administered 2 mg IV midazolam prior to entering the operating room. No opioid narcotics were administered until after the airway was secured with either a laryngeal mask airway (LMA) or endotracheal tube. Heat and moisture exchangers were used on all patients. Patients could receive up to 300 mL room
temperature intravenous crystalloid before fluid was warmed (Ranger, Arizant Healthcare, Eden Prairie, MN) to 41°C. All inductions, nasal temperature probe placement*, and application of a FAW blanket were performed in the same manner by the first author. Either an upper or lower body FAW blanket (SW-2010 Snuggle Warm Small Upper Body Convective Warming Blanket, or SW-2001 Snuggle Warm Adult Full Body Convective Warming Blanket, Level 1, Smiths Medical ASD, Rockland, MA) was used. The face was not directly covered by the FAW blanket in order to avoid the possibility that a collection of warm air could affect the nasal temperature measurements. Cotton blankets were placed on top of the warming blankets. The FAW (Equator Convective Warmer, Level 1, Smiths Medical ASD, Rockland, MA) was turned on to 44°C as soon as the patient was prepped and draped; the time duration from the start of induction (T₀) until the time the FAW was turned on was recorded. Neurophysiologic monitors to measure “depth of anesthesia” were not used. Pre-induction core temperatures were not measured.

*(Footnote) Nasal temperature was used as a surrogate for core temperature for all patients since it could be used for patients having either an LMA or endotracheal intubation. Previous work has shown a close agreement between the nasal technique used in this study and distal esophageal temperature measurements.  

Group INH/100 – Inhalation induction with sevoflurane in 100% oxygen (O₂)

A baseline blood pressure was taken prior to induction. No formal preoxygenation regimen was performed. The patients were asked to breath for a few breaths via the face mask with 100% O₂ just to confirm reservoir bag movement and capnograph detection of carbon dioxide. At time T₀, with an unprimed circuit, the O₂ flow meter was set at 6 LPM and the sevoflurane vaporizer was turned on at 8%. Blood pressures were recorded every
minute starting one minute after \( T_0 \) (\( T_1 \)) until airway intervention commenced. At the discretion of the first author, an LMA was inserted when the patient was assessed to be adequately deep, determined by masseter muscle relaxation, typically just two minutes after \( T_0 \) (\( T_2 \)). Alternatively, if the patient was to be endotracheally intubated, muscle relaxant (vecuronium, rocuronium, or succinylcholine) was administered when the patient was assessed as being unconscious, typically at \( T_1 \). Positive pressure ventilation was performed as required until endotracheal intubation. If necessary, to avoid hypotension, the Sevoflurane concentration was decreased while waiting for adequate muscle relaxation. If the systolic blood pressure dropped below 85 mm Hg prior to airway intervention, the patient would be treated immediately either with phenylephrine or airway intervention if ready. After securing either the LMA or endotracheal tube, anesthesia was maintained with sevoflurane in 50% nitrous oxide (1 LPM) and 50% \( O_2 \) (1 LPM). Opioid narcotics (fentanyl, hydromorphone, methadone), neuromuscular reversal agents (glycopyrrolate, neostigmine), dexamethasone, and ketamine were administered as per the discretion of the attending anesthesiologist.

Within 10 minutes of \( T_0 \), a nasal temperature probe modified from a skin temperature probe (Skin Temperature Sensor, 400 Series, DeRoyal Industries, Inc., Lane Powell, TN) was inserted 8 cm into one naris.\(^7\)-\(^9\) This provided a minimum of 5 minutes for thermal equilibration of the temperature probe before the first measurement (\( T_{15} \)), fifteen minutes after \( T_0 \). Either naris was used arbitrarily. Starting at \( T_{15} \), nasal temperatures were recorded every 15 minutes (\( T_{15}, T_{30}, T_{45}, T_{60} \)). If the core temperature reached 37.5°C, the FAW was turned off. The patient’s data were included in the analysis if there were at least two temperature measurements (\( T_{15} \) and \( T_{30} \)). If the anesthetic ended before 30 minutes or if there was a protocol violation, that patient’s data were not analyzed; a
replacement envelope assigning another future patient to that group was generated and inserted randomly back into the envelope stack. All patients received 4 mg ondansetron within 15 minutes of emergence. Temperature data collection ceased at the initiation of IV acetaminophen administration or if there was any event that could have a substantial impact on patient temperature. All cystoscopy procedures were conducted with warmed bladder irrigation.

Group INH/50 - Inhalation induction with sevoflurane in 50% nitrous oxide (N\textsubscript{2}O) / 50% O\textsubscript{2}

The protocol was identical to group INH/100 except that induction was performed with 3 LPM N\textsubscript{2}O and 3 LPM O\textsubscript{2} (instead of 6 LPM O\textsubscript{2}) with 8% sevoflurane.

Group PROP – Intravenous induction with intravenous propofol

The induction differed from group INH/100 in the following manner. Two mL of 2% lidocaine (40 mg) were added to 20 mL of 1% propofol. After preoxygenation with 100% O\textsubscript{2} for a minimum of 2 minutes, three mL of 2% lidocaine (60 mg) was administered followed immediately by 2.2 mg/kg propofol (rounded to the nearest 5 mg) at T\textsubscript{0}. If the patient was to receive an LMA, one blood pressure was taken at T\textsubscript{1} and then the LMA was inserted. If the patient was to be endotracheally intubated, muscle relaxant was administered immediately after propofol administration, blood pressures were measured every minute, and positive pressure ventilation with 100% O\textsubscript{2} was performed as required. After securing the airway, the protocol continued in the same manner as in Group INH/100.

Group Phnl/PROP – Intravenous induction with intravenous propofol preceded by
phenylephrine

The protocol differed from group PROP only in that 2 mL of 80 mcg/mL phenylephrine (160 mcg) was administered immediately after the administration of 3 mL 2% lidocaine but before the 2.2 mg/kg propofol.

STATISTICAL METHODS

To address the lack of pre-test core temperature measurements, we used the post-test only, single blind randomized trial. This is a “true experimental design”. The primary outcomes were the nasal (core) temperatures at 4 time points after induction (not changes from pre-induction baseline). In bivariate analyses, we compared differences in mean core temperature between the propofol only induction control group (PROP) and each of 3 groups administered alternative induction techniques (INH/100, INH/50, and Phnl/POR). Specifically, analyses of the mean temperature differences (and 95% CIs) for 1) INH/100 vs. PROP, 2) INH/50 vs. PROP, and 3) Phnl/POR vs. PROP were performed at each of 15, 30, 45, and 60 minutes ($T_{15}$, $T_{30}$, $T_{45}$, and $T_{60}$) after induction. These differences in mean core temperatures at $T_{15}$, $T_{30}$, $T_{45}$, and $T_{60}$ among groups were assessed using unpaired t-tests and corresponding 95% confidence intervals (95% CIs). Bonferroni’s correction was used to adjust for the 12 multiple comparisons. Core temperature data were tested for normality by the Shapiro-Wilk test.

The random assignment of 50 patients per group made it likely that the treatment groups would be balanced in both measured and unmeasured characteristics (including pre-induction core temperatures). However, imbalances did occur in BMI and sex. Those imbalances and the lack of pre-induction core temperature measurements necessitated a multivariable analysis comparing the average core temperatures at $T_{15}$, $T_{30}$, $T_{45}$, and $T_{60}$;
the covariates were BMI, sex, age, ASA classification, and time to initiating FAW. (Upper vs lower FAW were not covariates because the rates of heat transfers are similar.\textsuperscript{11}) This multivariable analysis was a linear mixed model with random intercepts and random slopes and unstructured covariance. This model fit better than a model with random intercepts alone nested within it (p<0.0001 by the likelihood ratio test).\textsuperscript{12} There was no statistically significant interaction between group and time (p=0.15). Since the results of the bivariate and multivariable analyses were similar and led to the same conclusions, we present the simpler bivariate results. The differences in the secondary outcomes, the percentages of patients who had at least one temperature <36.0°C (and ≤35.5°C) between the control group (PROP) and each of the other three groups were evaluated by Fisher’s exact tests. Although the resulting p values were exact; the corresponding 95% CIs were approximate.

Interval estimates of the percentages of patients that developed hypotension requiring treatment and of patients undergoing an inhalation induction who developed apnea were computed using exact binomial 95% CIs.

A statistical power analysis suggested that 34 patients per group were needed to detect a mean core temperature difference of 0.5°C with standard deviation=0.5°C at alpha=0.05 with 80% power in a two-sided test. We studied 50 patients in each group anticipating patient loss after T\textsubscript{30}. All statistical analyses compared patients as treated using two-sided tests with alpha=0.05 and were performed using Stata, version 14 (Stata Press, College Station, Texas).

Results

After randomization and withdrawals, 50 patients in each group were analyzed (Figure 1). Demographic and forced air warming data are presented in Table 3. The surgical
procedures are presented in Table 4.

Compared to group PROP, the three alternative induction groups each had higher mean core temperatures and fewer patients having at least one core temperature measurement <36.0°C in the first hour. At all four time points (T₁₅, T₃₀, T₄₅, T₆₀), the mean temperatures in group PROP were between 0.39 and 0.54°C lower than in groups INH/100, INH/50 and Phnl/PROP (all p≤0.006 adjusted for multiple comparisons, Figure 2, Table 5). There were no statistically significant differences in the mean temperatures between groups INH/100 and INH/50, INH/100 and Phyl/PROP, and INH/50 and Phyl/PROP at any time point (all p>0.18). In group PROP, 60% of patients had at least one temperature <36.0°C in the first hour compared to 16% in each of groups INH/100, INH/50, and Phnl/PROP (all with an identical 44 percentage point difference, 95% CI 27% to 61%, p<0.0001). In group PROP, 22% of patients had at least one temperature ≤35.5°C, compared to 8% in group INH/100 (p=0.09), 4% in INH/50 (p=0.015), and 2% in Phnl/PROP (p=0.004).

No patient in any of these 4 groups had a core temperature >37.5°C at any time point. Apnea did not occur in either group INH/100 or INH/50 (0%, 95% CI 0% to 7.1% for each group).

Only blood pressures at T₁ (and T₂ if prior to airway intervention) were considered. In the first 2 minutes, treatment of hypotension (systolic BP < 85 mm Hg) was required in 2 patients in Group PROP (4%, 95% CI 0.5% to 13.7%) and 1 patient in group Phnl/PROP (2%, 95% CI 0.05% to 10.6%). In group Phnl/PROP, only 1 patient's blood pressure increased to a value >180 mm Hg and no patient suffered a reflex bradycardia ≤40 beats per minute. No patients in groups INH/100 or INH/50 (0%, 95% CI 0% to 7.1% for each group) required treatment for hypotension.

Discussion
This effectiveness study found that in patients aged 18 to 55 years, inhalation inductions with sevoflurane or the administration of 160 mcg phenylephrine immediately prior to 2.2 mg/kg propofol each caused less redistribution hypothermia than intravenous inductions with propofol alone.

This study's results are consistent with previous work\textsuperscript{3,4} and thus provide support for this study's conclusion. Ikeda found a 0.7°C average thermal advantage of sevoflurane inhalation inductions over intravenous propofol.\textsuperscript{3} We found a slightly smaller (0.4°C to 0.5°C) advantage. That may reflect the use of forced air warming whereas Ikeda did not use FAW.\textsuperscript{3} Also, Ikeda used a larger dose of propofol, which might have caused more vasodilation and thus more redistribution hypothermia. Sun found 64% of 58,814 patients had a temperature <36°C after 45 minutes, close to the 60% in group PROP; 29% were <35.5°C, close to the 22% in group PROP.\textsuperscript{4} The small differences in results in these studies may in part reflect Sun's patients having a higher mean age than study group PROP and/or random variation. Older patients have an increased risk for hypothermia.\textsuperscript{8,13,14}

Without patient warming, temperature decreases can continue for 3 hours.\textsuperscript{15} With the prompt initiation of forced air warming, we found most of the redistribution hypothermia occurred in the first 15 minutes. Within each group, the differences in mean core temperature between $T_{15}$ and $T_{30}$, $T_{30}$ and $T_{45}$, and $T_{45}$ and $T_{60}$ were small and clinically insignificant (Figure 2).

We found a bolus dose of phenylephrine reduced redistribution hypothermia. Ikeda et al found intraoperative phenylephrine infusion decreased the magnitude of redistribution hypothermia.\textsuperscript{16} Ikeda concluded that even a short period of vasodilation can result in
redistribution hypothermia.\textsuperscript{3} The phenylephrine bolus opposed enough of the propofol induced vasodilation to reduce the amount of redistribution hypothermia. We administered a prior bolus dose of phenylephrine (about 10 seconds before propofol) without an infusion. Whether phenylephrine would be as effective if given after the propofol is not known. First, some vasodilation and heat transfer might have already occurred, and second, it is unknown if there is the same resultant vasodilation when phenylephrine is given after propofol.

Techniques that can reduce redistribution hypothermia now include prewarming\textsuperscript{17-21}, ketamine\textsuperscript{22}, etomidate\textsuperscript{23}, phenylephrine infusions\textsuperscript{16}, amino acid infusions\textsuperscript{24}, fructose\textsuperscript{25}, inhalation inductions\textsuperscript{3}, and bolus phenylephrine prior to propofol. None of these techniques solve the hypothermia problem fully. Combinations of these techniques may result in additional thermal benefit but have not been studied.

Inhalation inductions were performed gradually (i.e., without a primed circuit) for two reasons. First, apnea is unlikely to occur. Apnea never occurred in the 100 inhalation patients. Second, gradually increasing anesthetic depth likely contributes to hemodynamic stability, a potential benefit of inhalation inductions. Thwaites concluded that inhalation inductions were more hemodynamically stable than IV propofol inductions.\textsuperscript{26} Retrospective studies found that adverse outcomes were associated with even short periods of hypotension, but not hypertension.\textsuperscript{27,28} Maheshwari et al recently found that a substantial fraction of all hypotension occurred before surgical incision as a result of anesthetic management; this hypotension was associated with postoperative kidney injury.\textsuperscript{29} We observed no hypotension (systolic BP <85 mm Hg) in any inhalation induction patient. Hypotension can occur rapidly with intravenous propofol inductions. Decreases in blood pressure with inhalation inductions are usually more gradual. Such
gradual decreases could be addressed earlier, or prophylactically, before there is clinically important hypotension.

We found 160 mcg phenylephrine to be an effective dose in most Phnl/PROP patients. Small percentages of Phnl/PROP patients had a post-induction systolic blood pressure either <85 mm Hg or >180 mm Hg. An optimal phenylephrine dose (e.g., weight based) would minimize hypo- and hypertension events and still maintain the thermal benefit. We studied only one dose of phenylephrine.

In the multivariable analysis, neither BMI nor sex was associated with the degree of redistribution hypothermia. This indicates that differences in BMI and sex between treatment groups were not responsible for the differences in mean core temperatures (redistribution hypothermia) between groups. We found patients were susceptible to redistribution hypothermia regardless of BMI. Because it takes more heat transfer to change the temperature of a heavier patient, it is commonly believed that obese patients are more resistant to temperature change. However, a different process is dominant during the initial redistribution hypothermia phase. Many obese patients have substantial muscle mass in their periphery to move their heavy body parts. The relatively little blood flow in adipose tissue may prevent meaningful temperature buffering during the redistribution hypothermia phase.

LIMITATIONS

We studied hypothermia during surgery, not surgical outcome. Since hypothermia causes adverse outcomes\textsuperscript{1,2}, it is plausible that the studied alternative induction techniques will result in superior clinical outcomes than propofol by keeping patients warmer. It remains to conduct randomized controlled trials addressing whether clinical outcomes improve using one of the alternative induction techniques.
Although our results suggest a possible hemodynamic benefit of these alternative induction techniques, many more patients need to be studied to demonstrate that benefit. Having one caregiver (the first author) performing the randomization, providing anesthetic care, and recording outcomes is a potential source of bias. The study design addressed these issues. Since the next study patient was already in the operating room at the time of random assignment, the caregiver could not affect the random allocation. By having a single caregiver, the manner of induction and all the tasks performed at the beginning of the case were more uniform than if the tasks were performed by multiple caregivers. The temperatures recorded were objective and not affected by who recorded the data. We did not control for “depth of anesthesia”. A greater depth of anesthesia likely results in more vasodilation and thus more redistribution hypothermia (and hypotension). If inductions achieve only the minimum necessary depth, it is plausible there may be less redistribution hypothermia (and hypotension). In this effectiveness study, we titrated the maintenance dose of anesthetic by vital signs, as is common in clinical practice. Titrating anesthetic doses to anesthetic depth may yield different results. A given depth of anesthesia can be achieved by varying the type and dose of anesthesia. We studied only one dose of propofol. It is plausible that using a lower dose of propofol and/or sevoflurane for induction will result in less redistribution hypothermia. Kazama et al demonstrated that anesthetic inductions can be accomplished with a smaller dose of propofol than used in this study.\textsuperscript{30} There were a variety of different surgeries, but no major intraabdominal or intrathoracic surgeries (with their greater potential for intraoperative heat loss). Since patients with different surgeries were treated similarly and had comparable thermal exposure in the first 15 minutes post induction, the impact of the specific surgery should be minor. We did not study intrathoracic or major intraabdominal surgeries where there is greater
thermal stress. We can make no statement as to whether the initial thermal benefit is well maintained in such cases.

We did not measure pre-induction core temperatures. Although studies similar to this one often compare the changes from baseline temperature, we did not. We measured the core temperatures at 4 times after induction. To address the lack of pre-test core temperature measurements, we used a post-test only randomized trial. Our experimental design, while less common, “contains no threats to internal validity”.\textsuperscript{10}

We performed “as treated” analyses on 200 of the 205 (97.6\%) randomized patients. Those 5 excluded patients provided no valid temperature data. Four patients had no post-induction temperature measurements because they were withdrawn before $T_{15}$. In one patient, there was only one temperature measurement at $T_{15}$. This patient received more than 300 mL unwarmed IV fluid. This makes it very unlikely that the results differ substantially from an intention-to-treat analysis. With the exclusion of these five patients, the 200 patients presented in Table 3 are exactly those we analyzed. Thus, the randomization combined with the bivariate and multivariable statistical results support the study conclusion that the three alternative inductions produced higher temperatures than propofol alone.

Conclusions

This study makes evident the thermal benefits of inhalation inductions and prophylactic bolus phenylephrine administration over standard intravenous propofol alone inductions in adults age 18 to 55 inclusive. This offers quick, simple and easy to use partial solutions to the on-going problem of intraoperative hypothermia.

Abbreviations

BMI – body mass index
BP – blood pressure

C – centigrade

CI – confidence interval

FAW – forced air warming

Hg – mercury

INH/50 – study group induced with 50% oxygen and 50% nitrous oxide

INH/100 - study group induced with 100% oxygen

IV – intravenous

kg – kilogram

LMA – laryngeal mask airway

LPM – liters per minute

m – meter

mcg – microgram

mg – milligram

mL – milliliter

mm – millimeter

N₂O – nitrous oxide

O₂ – oxygen

Phnl/PROP - study group induced with 160 mcg phenylephrine followed by 2.2 mg/kg IV propofol

PROP – study group induced with 2.2 mg/kg IV propofol

SD – standard deviation

Tₓ – time x minutes after the start of anesthetic induction

Declarations
Ethics approval and consent to participate

This study and consent forms were approved by our IRB and submitted to clinical-trials.gov as NCT02331108 by Jonathan V. Roth on November 20, 2014. Informed consent was obtained from all participating patients.

Consent for publication

Not applicable

Availability of data and material

We will make our data available on the NCT (clinical-trials.gov) repository.

Competing interests

The authors declare that they have no competing interests

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Authors contributions

Leonard Braitman:

Power study back in 2014. Statistical calculations. Wrote the statistical methods section and much of the results section. Overall review and edits for clarity. Made suggestions for tables and figures. Response to reviewers.

Lacy H. Hunt:

Statistical calculations. Suggestions for methods and results sections, tables, and figures. Overall review and edits for clarity.

Jonathan Roth:

(Everything else.) Background research. Generation of idea. Generated protocol. IRB approval. Periodic reporting to IRB. Registered on clinical-trials.gov. Creation of randomized envelopes. Obtained consent for every patient. Performed induction and
other required tasks for every patient. Data collection and entered into EXCEL worksheets. Basic analysis and data preparation/organization for statisticians. Writing of manuscript. Submission to journal. Response to reviewers.

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Author information

None

References

1. Sessler DI. Complications and treatment of mild hypothermia. Anesthesiology. 2001; 95:531-543.

2. Stewart PA, Liang SS, Li QS, Huang ML, Bilgin AB, Kim D, Phillips S. The impact of residual neuromuscular blockade, oversedation, and hypothermia on adverse respiratory events in a postanesthetic care unit: A prospective study of prevalence, predictors, and outcomes. Anesth Analg. 2016; 123(4):859-868.

3. 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; 88:921-924.

4. Sun Z, Honar H, Sessler DI, Dalton JE, Yang D, Panjasawatwong K, Deroee AF, Salmasi V, Saager L, Kurz A. Intraoperative core temperature patterns, transfusion requirement, and hospital duration in patients warmed with forced air. Anesthesiology. 2015; 122:276-285.

5. Winkler M, Akca O, Birkenberg B, Hetz H, Scheck T, Arkilic CF, Kabon B, Marker E, Gru A, Czepan R, Greher M, Goll V, Gottsauner-Wolf F, Kurz A, sessler DI. Aggressive warming reduces blood loss during hip arthroplasty. Anesth Analg. 2000; 91:978-984.

6. Rajagopalan S, Mascha E, Na J, Sessler DI. The effects of mild perioperative...
hypothermia on blood loss and transfusion requirement. Anesthesiology. 2008; 108:71-77.

7. Roth JV, Braitman LE. Nasal temperature can be used as a reliable surrogate measure of core temperature. Journal of Clinical Monitoring and Computing. 2008; 22:309-314.

8. Sessler DI. Temperature Monitoring and Perioperative Thermoregulation. Anesthesiology. 2008; 109(2):318-338.

9. Wang M, Singh A, Qureshi H, Leone A, Mascha EJ, Sessler DI. Optimal Depth for Nasopharyngeal Temperature Probe Positioning. Anesth Analg. 2016; 122:1434-1438.

10. D.T. Campbell and J.C. Stanley. Experimental and Quasi-experimental designs for research. Houghton Mifflin Company 1963, page 8.

11. Giesbrecht GG, Ducharme MB, McGuire JP: Comparison of Forced-air Warming Systems for Perioperative Use. Anesthesiology 1994; 80:671-9.

12. Hoffman L. Longitudinal Analysis- Modelling Within-Person Fluctuation and Change. New York: Routledge, 2015; pages 101-3, 152-3.

13. Vaughan MS, Vaughan RW, Cook RC. Postoperative hypothermia in adults: Relationship of age, anesthesia, and shivering to rewarming. Anesth Analg. 1981; 60:746-751.

14. Ozaki M, Sessler DI, Suzuki H, Ozaki K, Tsunoda C, Atarashi K: Nitrous oxide decreases the threshold for vasoconstriction less than sevoflurane or isoflurance. Anesth Analg. 1995; 80: 1212-1216.

15. Matsukawa T, Sessler DI, Sessler AM, Schroeder M, Ozaki M, Kurz A, Cheng C. Heat Flow and Distribution during Induction of General Anesthesia. Anesthesiology. 1995; 82:662-673.

16. Ikeda T, Ozaki M, Sessler DI, Kazama T, Ikeda K, Sato S. Intraoperative phenylephrine infusion decreases the magnitude of redistribution hypothermia. Anesth Analg. 1999;
17. Just B, Trevien V, Lelva E, Lienhart A. Prevention of intraoperative hypothermia by preoperative skin-surface warming. Anesthesiology. 1993; 79:214-218.

18. Andrzejowski J, Hoyle J, eapen G, Turnbull D. Effect of prewarming on post-induction core temperature and the incidence of inadvertent perioperative hypothermia in patients undergoing general anaesthesia. Br. J. Anaesth. 2008; 101:627-631.

19. Bock M, Muller J, Bach A, Bohrer H, Martin E, Motsch J. Effects of preinduction and intraoperative warming during major laparotomy. Br. J. Anaesth. 1998; 80:159-163.

20. Camus Y, Delva E, Sessler DI, Lienhart A. Pre-induction skin-surface warming minimizes intraoperative core hypothermia. Journal of Clinical Anesthesia. 1995; 7:384-388.

21. Hynson JM, Sessler DI, Moayeri A, McGuire J, Schroeder BS. The effects of preinduction warming on temperature and blood pressure during propofol-nitrous oxide anesthesia. Anesthesiology. 1993; 79:219-228.

22. Ikeda T, Kazama T, Sessler DI, Toriyama S, Niwa K, Shimada C, Sato S. Induction of anesthesia with ketamine reduces the magnitude of redistribution hypothermia. Anesth Analg. 2001; 93:934-938.

23. Park HP, Kang JM, Jeon YT, Choi IY, Oh YS, Hwang JW. Comparison of the effects of etomidate and propofol on redistribution hypothermia during general anesthesia. Korean J Anesthesiol. 2006; 50:S19-S24.

24. Aoki Y, Aoshima Y, Atsumi K, Kaminaka R, Nakau R, Yanagida K, Kora M, Fujii S, Yokoyama J. Perioperative Amino Acid Infusion for Preventing Hypothermia and Improving Clinical Outcomes During Surgery Unger General Anesthesia: A Systematic Review and Meta-analysis. Anesth Analg. 2017; 125:793-802.

25. Mizobe T, Nakajima Y, Ueno H, Sessler DI: Fructose administration increases
intraoperative core temperature by augmenting both metabolic rate and the vasoconstriction threshold. Anesthesiology 2006; 104:1124-30.

26. Thwaites A, Edmonds S, and Smith I. Inhalation induction with sevoflurane: a double-blind comparison with propofol. Br. J. Anaesth. 1997; 78:356-361.

27. Monk TG, Bronsert MR, Henderson WG, Mangione MP, Sum-Ping ST, Bentt DR, Nguyen JD, Richman JS, Mequid RA, Hammermeister KE. Association between Intraoperative Hypotension and Hypertension and 30-day Postoperative Mortality in Noncardiac Surgery. Anesthesiology. 2015; 123:307-319.

28. Walsh M, Devereaux PJ, Garg AX, Kurz A, Turan A, Rodseth RN, Cywinski J, Thabane L, Sessler DI. Relationship between Intraoperative Mean Arterial Blood Pressure and Clinical Outcomes after Noncardiac Surgery: Toward an Empirical Definition of Hypotension. Anesthesiology. 2013; 119:507-515.

29. Maheshwari K, Turan A, Mao G, Yang D, Niazi AK, Agarwal D, Sessler DI, Kurz A: The association of hypotension during non-cardiac surgery, before and after skin incision, with postoperative acute injury: a retrospective cohort analysis. Anaesthesia 2018;73:1223-1228.

30. Kazama T, Ikeda K, Morita K, Kikura M, Ikeda T, Kurita T, Sato S. Investigation of Effective Anesthesia Induction Doses Using a Wide Range of Infusion Rates with Undiluted and Diluted Propofol. Anesthesiology. 2000; 92:1017-1028.

31. Ozaki M, Sessler DI, Suzuki H, Ozaki K, Tsunoda C, Atarashi K: Nitrous oxide decreases the threshold for vasoconstriction less than sevoflurane or isoflurane. Anesth Analg. 1995; 80: 1212-1216.

Tables

Table 1 – Study groups

| Group   | Induction technique |
|---------|---------------------|

21
INH/100  Inhalation: 8% sevoflurane in 100% oxygen

INH/50  Inhalation: 8% sevoflurane in 50% oxygen and 50% nitrous oxide*

PROP  Intravenous: 2.2 mg Propofol

Phyl/PROP  Intravenous: 2.2 mg propofol preceded by 160 mcg phenylephrine

* Nitrous oxide may have vasoconstricting effects. Thus, for a given depth of anesthesia, there may be less vasodilation in a N₂O /sevoflurane anesthetic due to a lesser amount of sevoflurane than in a sevoflurane induction without N₂O. Ozaki et al found N₂O impairs thermoregulation less than sevoflurane or isoflurane. With less vasodilation, it seemed plausible that there would be less redistribution hypothermia if N₂O was used; hence the reason for studying inhalation inductions using both 100% O₂ and 50% O₂ / 50% N₂O.

Table 2 – Inclusion and exclusion criteria

INCLUSION CRITERIA

Age 18 to 55 years inclusive
Scheduled for general anesthesia where 50% nitrous oxide in oxygen could be used
Endotracheal intubation or laryngeal mask airway insertion would be used
Afebrile (preoperative oral or temporal scan temperature between 36.2 and 37.4°C inclusive)
Positioned supine or lithotomy
Forced air warming would be used
Expected duration of anesthetic to be at least 60 minutes

EXCLUSION CRITERIA
Emergency surgery or any other aspiration risk
Age <18 years or >55 years
Pregnant
Incarceration
Febrile illness
Anticipated difficult airway
Contraindication to nitrous oxide use
Contraindication to nasal instrumentation
Nasal surgery
Current or recent epistaxis
Requirement for foreign language interpreter
Allergy to propofol
Malignant hyperthermia risk
Inability to oxygenate on less than 50% oxygen
Cardiac surgery
Neuro-surgery
Receiving vasoactive infusions
Significant valvular heart disease
Unstable cardiac disease
Requiring prone or lateral positioning
Inability to provide informed consent
Inability to use forced air warming
Untreated hypo- or hyper-thyroidism
ASA class 4, 5 or 6*
Anticipated inability to tolerate any of the 4 different anesthetic induction options in this study

*Patients with end stage renal disease on dialysis were classified as ASA 3.

Table 3 Demographics and forced air warming data of the 200 patients analyzed

| Group          | INH/100 | INH/50 | PROP   | Phnl/PROP |
|----------------|---------|--------|--------|-----------|
| Age (years)    |         |        |        |           |
| Mean (SD)      | 42.8 (10.1) | 43.0 (8.6) | 39.0 (11.2) | 40.6 (9.1) |
| Range          | 22 to 55 | 26 to 55 | 18 to 55 | 20 to 55  |
| Sex            |         |        |        |           |
| Male n (%)     | 20 (40) | 31 (62) | 20 (40) | 21 (42)   |
| ASA classification |     |        |        |           |
| 1 n (%)        | 1 (2)   | 3 (6)  | 10 (20) | 2 (4)     |
2  n (%)  23 (46)  23 (46)  29 (58)  33 (66)
3  n (%)  16 (52)  24 (48)  11 (22)  15 (30)

BMI (kg/m²)

Mean (SD)  31.9 (7.5)  31.2 (6.7)  26.8 (5.6)  29.9 (6.4)
Range  21.7 to 48.9  18.9 to 44.2  17.2 to 43.0  15.1 to 44.4

Preoperative screening temperature (°C)

Mean (SD)  36.8 (0.3)  36.8 (0.3)  36.8 (0.3)  36.7 (0.3)

Use of upper body forced air warming (FAW) blanket

(remaining patients used lower body FAW)

n  32  39  29  30
n (%)  (64)  (78)  (58)  (60)

Time from T₀ until FAW turned on, (minutes)

Mean (SD)  16.4 (7.0)  14.7 (7.0)  15.9 (7.9)  17.1 (7.7)
Range  5 to 45  4 to 45  4 to 44  6 to 40

Table 4 – List of surgeries

Procedure  Groups having at least one patient having the listed procedure are denoted by an x

|                  | INH/100 | INH/50 | PROP | PhnI/PROP |
|------------------|---------|--------|------|-----------|
| **UROLOGIC**     |         |        |      |           |
| Cystoscopic surgery | x     | x      | x    | x         |
| Penile procedures | x      | x      |      | x         |
| Suprapubic tube placement | x    |        |      |           |

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| Procedure                                                      |   |
|---------------------------------------------------------------|---|
| Scrotal procedures                                            | x |
| Urethroplasty                                                 | x | x | x | x |
| **ORTHOPEDIC**                                                |   |
| Lower extremity orthopedics                                  | x | x | x | x | x |
| Upper extremity orthopedics                                  | x | x | x | x | x |
| Anterior cervical disectomy and fusion                        | x |
| **GYNECOLOGIC**                                               |   |
| Vulvoplasty or excision of lesion                             | x | x |
| Dilation and curettage, hysteroscopy                          | x | x | x | x | x |
| Loop endocervical excision procedure                          | x | x |
| Endocervical curettage                                        | x | x |
| Hysterectomy                                                  | x | x | x | x |
| Myomectomy                                                    | x | x | x | x |
| **VASCULAR**                                                  |   |
| Dialysis access related procedures                            | x | x | x | x | x |
| Lower extremity vascular – open procedures                    | x |
| Radiofrequency ablation and/or Lower extremity phlebectomies  | x | x | x | x |
| Lower extremity amputations                                  | x | x |
| **DENTAL/ENT**                                                 |   |
|                                                               | x | x | x | x |
THORACIC

Endobronchial ultrasound  x  x  x

GENERAL SURGERY

Vacuum assisted closure change  x

Non-cavitary procedures  x  x  x

Inguinal hernia  x

Breast  x  x  x  x  x

Table 5  Differences between the mean core temperature (°C) of each of three alternative induction groups and the standard propofol alone group at each time point*

| Comparison groups | T<sub>15</sub> | T<sub>30</sub> | T<sub>45</sub> | T<sub>60</sub> |
|-------------------|---------------|---------------|---------------|---------------|
| INH/100 minus PROP |                |               |               |               |
| Difference (°C)   | 0.46          | 0.46          | 0.47          | 0.49          |
| 95% CI of difference | 0.28 to 0.64 | 0.28 to 0.64 | 0.25 to 0.69 | 0.20 to 0.77 |
| INH/50 minus PROP |                |               |               |               |
| Difference (°C)   | 0.47**        | 0.52**        | 0.50          | 0.54          |
| 95% CI of difference | 0.31 to 0.64 | 0.36 to 0.69 | 0.31 to 0.69 | 0.28 to 0.79 |
| PhnI/PROP minus PROP |            |               |               |               |
| Difference (°C)   | 0.39          | 0.41          | 0.45          | 0.47**        |
| 95% CI of difference | 0.24 to 0.54 | 0.25 to 0.57 | 0.27 to 0.63 | 0.25 to 0.70 |
*p ≤ 0.001 for each of the above comparisons separately. p ≤ 0.006 when applying Bonferroni’s correction for the 12 multiple comparisons (3 groups compared to propofol only group at 4 time points).

**These differences are correct to 2 decimal places. Because of rounding to two decimal places in Figure 2, they differ by 0.01 from those that would be calculated using Figure 2.

Figures
Eleven patients consented but were never randomized and not studied: 9: The first author was not available to perform the induction 1: The case changed from a general anesthetic to a sedation case 1: The surgeon did not want that patient to be in a clinical study. Five patients were induced and then withdrawn from analysis* because of protocol violations: 1: Airway difficulty during induction 1: Additional propofol required 2: Patients received more than 300 mL unwarmed IV fluid 1: Forced air warming malfunction *Four patients were withdrawn before T15 so that they had no post-induction temperature measurements. In one patient, there was only one temperature measurement at T15. This patient received more than 300 mL unwarmed IV fluid.
### Mean Temperature ± SD and Number (n) in Each Group at Each Time Point (°C)

|                  | T15          | T30          | T45          | T60          |
|------------------|--------------|--------------|--------------|--------------|
| INH/100          | 36.42 ± 0.49 (50) | 36.41 ± 0.49 (50) | 36.47 ± 0.53 (37) | 36.52 ± 0.56 (27) |
| INH/50           | 36.44 ± 0.44 (50) | 36.48 ± 0.44 (50) | 36.50 ± 0.45 (41) | 36.57 ± 0.42 (28) |
| PROP             | 35.96 ± 0.40 (50) | 35.95 ± 0.41 (50) | 36.00 ± 0.45 (43) | 36.03 ± 0.53 (32) |
| PhnI/PROP        | 36.35 ± 0.38 (50) | 36.36 ± 0.40 (50) | 36.45 ± 0.40 (45) | 36.51 ± 0.40 (40) |

**Figure 2**
Mean Temperature ± SD and Number (n) in Each Group at Each Time Point (°C)
Legend/caption In the three successive time intervals (T15 to T30, T30 to T45, and T45 to T60), the percentage of patients (all groups combined) whose temperature decreased were (37.5%, 14.4%, and 14.2% respectively). The percentage of patients whose temperature increased were (39.0%, 55.4%, and 59.1% respectively). The remaining patients had no temperature changes within these time intervals.