

Induction techniques that reduce redistribution hypothermia: A prospective, randomized, controlled, single blind 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 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. (Inhalation inductions only were also studied in patients age >55 years.) **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<0.0001 for all comparisons), averaging between 0.39oC and 0.54oC higher. In group PROP, 60% of patients had at least one temperature below 36.0oC 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). (Inhalation inductions were also effective in reducing redistribution hypothermia in patients age >55 years.) **CONCLUSIONS** Inhalation inductions with sevoflurane or 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. Registered on clinical-trials.gov as NCT02331108, November 20, 2014.

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. The American College of Surgeons consider intraoperative hypothermia to be a modifiable risk factor for surgical site infections; they recommend the maintenance of intraoperative normothermia and the use of prewarming.³ The 2017 CDC guidelines recommend maintenance of perioperative normothermia.⁴

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).⁵⁻⁷ The contribution of intraoperative hypothermia to postoperative complications may often 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.

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.⁸ Sun et al documented that hypothermia is routine during the first hour of anesthesia.⁵ Printed on the cover of the February 2015 issue of *Anesthesiology* was “Despite Active Warming Hypothermia is Routine in the First Hour of Anesthesia”. Hopf has called for studies to evaluate 1) the effectiveness of interventions to reduce the degree and duration of intraoperative hypothermia, and 2) the effect of these interventions on the broad range of patient outcomes known to be temperature sensitive.⁹ This study addresses the first part of her appeal.

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. It is reasonable to expect that inductions that cause less vasodilation will result in a lesser amount of redistribution hypothermia and less hypotension. The primary focus of this study is to compare the effect of alternative induction techniques on core temperature during the first hour of anesthesia in patients aged 18 to 55 years. Core temperatures using different anesthetic techniques (two inhalation techniques, one an alternative intravenous technique), believed to cause less vasodilation than IV propofol inductions, were each compared to those in patients receiving standard IV propofol anesthetic inductions.

As a secondary outcome, we compared the percentages of patients who had at least one core temperature reading below 36.0°C and at least one below 35.5°C in the first hour. The 36.0°C and 35.5°C temperature thresholds are meaningful because, 1) complications from hypothermia have generally been demonstrated when end of case core temperature decreases below 36°C, and 2) in the United States, the new MACRA (The Medicare Access and CHIP Reauthorization Act of 2015) standard is now 35.5°C.¹⁰

Compared to younger patients, older patients have an increased risk for hypothermia.¹¹⁻¹³ Thus we studied inhalation inductions in patients age >55 years as an exploratory secondary outcome. Because the dose of propofol would need to decrease and vary in elderly patients, we chose to study only inhalation inductions in patients aged >55 years. The older inhalation patients were compared to the younger inhalation patients to examine the effect of age. In addition, to demonstrate effectiveness of inhalation inductions in reducing redistribution hypothermia in older patients, the older inhalation patients (presumably at greater risk of hypothermia due to age) were compared to the younger propofol patients (presumably at lesser risk of hypothermia due to age).

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.

The six groups of 50 patients each are described in Table 1. Inclusion and exclusion criteria are presented in Table 2. After enrollment, patients were randomly assigned to one of their age appropriate groups. Random assignments were contained in opaque envelopes that were opened immediately before induction of anesthesia. Each of the envelopes contained one of the six group designations, 50 envelopes for each group. Separate randomization for each age group was achieved by putting the age appropriate envelopes in either the 18 to 55 year (n=200) basket or the >55 year (n=100) basket and mechanically mixing the envelopes within each basket. The envelopes were then randomly removed and put into the age appropriate stack. 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. All operating rooms had the same air flow design. Patients were allowed to receive up to 300 mL room temperature intravenous crystalloid before fluid was warmed (Ranger, Arizant Healthcare, Eden Prairie, MN) to 41°C. 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. All inductions, nasal temperature probe placement, and application of a forced air warming (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 (T_0) until the time the FAW was turned on was recorded. Neurophysiologic monitors to measure “depth of anesthesia” were not used.

Group INH/100 (A) – Inhalation induction with sevoflurane in 100% oxygen (O_2), age 18 to 55 years inclusive.

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% O_2 just to confirm reservoir bag movement and capnograph detection of carbon dioxide. At time T_0 , with an unprimed circuit, the O_2 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. Sevoflurane

concentration was decreased if necessary 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% O₂ (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 T₀, 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.^{13,15} This provided a minimum of 5 minutes for thermal equilibration of the temperature probe before the first measurement (T₁₅), fifteen minutes after T₀. Either naris was used arbitrarily. Starting at T₁₅, nasal temperatures were recorded every 15 minutes (T₁₅, T₃₀, T₄₅, T₆₀). 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 (T₁₅ and T₃₀). 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. This enabled us to assure we analyzed 50 patients in each group. 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 (B) - Inhalation induction with sevoflurane in 50% nitrous oxide (N₂O) / 50% O₂, age 18 to 55 years inclusive

The protocol was identical to group INH/100 except that induction was performed with 3 LPM N₂O and 3 LPM O₂ (instead of 6 LPM O₂) with 8% sevoflurane.

Group PROP (C) – Intravenous induction with intravenous propofol, age 18 to 55 years inclusive.

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% O₂ 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 T₀. If the patient was to receive an LMA, one blood pressure was taken at T₁ 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% O₂ was performed as required. After securing the airway, the protocol continued in the same manner as in Group INH/100.

Group Phnl/PROP (D) – Intravenous induction with intravenous propofol preceded by phenylephrine, age 18 to 55 years inclusive.

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.

Group INH/100>55 (AA) - Inhalation induction with sevoflurane in 100% O₂, age > 55 years.

At the discretion of the attending anesthesiologist, the patient may have received a reduced dose of midazolam. Otherwise, except for the age of the patients, the protocol was identical to group INH/100.

Group INH/50>55 (BB) – Inhalation induction with sevoflurane in 50% N₂O / 50% O₂, age > 55 years.

At the discretion of the attending anesthesiologist, the patient may have received a reduced dose of midazolam. Otherwise, except for the age of the patients, the protocol was identical to group INH/50.

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.

Results for patients aged 18 to 55 years

Compared to group PROP, the three alternative induction groups 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<0.001, Figure 2, Table 5). There were no statistical 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 p<0.0001, Table 6). The percentages of patients having at least one temperature <36.0°C in the first hour were identical in groups INH/100, INH/50, and Phnl/PROP. 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.

Only blood pressures at T₁ (and T₂ if prior to airway intervention) were considered. In Group PROP, 49 out of 50 patients had one or both post induction blood pressures decrease. In Group Phnl/PROP, 25 patients had one or both blood pressures decrease, 21 patients had one or both blood pressures increase, and 4 patients had one blood pressure higher and one lower than the pre-induction measurement. 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%). No patients in groups INH/100 or INH/50 (0%, 95% CI 0% to 7.1% for each group) required treatment for hypotension. 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. Apnea did not occur in either group INH/100 or INH/50 (0%, 95% CI 0% to 7.1% for each group).

Results that included patients aged >55 years

The older inhalationally induced patients had higher mean temperatures than the younger patients induced with propofol alone at all four time points; these mean differences ranged from 0.29°C to 0.44°C (all $p \leq 0.02$, Table 7, Figure 2). There were no statistical differences in the mean core temperatures between the older inhalation groups and the younger inhalation groups (INH/100 vs INH/100>55 and INH/50 vs INH/50>55, all $p \geq 0.12$). There were no statistical differences in the mean core temperatures between INH/100>55 and INH/50>55 at any of the four time points (all $p > 0.3$).

Both older inhalationally induced groups had 28% of patients with at least one temperature $< 36.0^\circ\text{C}$ compared to 60% in the younger propofol alone induced patients (Table 8), a 32 percentage point (95%CI, 14% to 50%; $p=0.002$) advantage for the older groups. There were no such statistical differences between the younger and older inhalation groups ($p=0.23$). Except for 1 patient in Group INH50>55 who had a core temperature of 37.6°C at one time point (T_{45}), no patient in any of the older groups had a core temperature $> 37.5^\circ\text{C}$ at any time point.

No patients in groups INH/100>55 or INH/50>55 had a systolic blood pressure < 85 mm Hg in the first two minutes of induction (0%, 95% CI 0% to 7.1 %), nor did any become apneic (0%, 95% CI 0% to 7.1%).

Discussion

This study found that in patients aged 18 to 55 years, inhalation inductions with sevoflurane and 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. Since hypothermia causes adverse outcomes¹, it is plausible that changing induction technique will result in improved outcomes by keeping patients warmer. A limitation of this study is that we studied hypothermia during surgery, not surgical outcome. It remains to conduct randomized controlled trials demonstrating that clinical outcomes improve using the alternatives we studied compared to propofol alone inductions.

This study's results are consistent with previous work.^{5,8} We found a 0.4°C to 0.5°C average thermal advantage of inhalation inductions over intravenous propofol while Ikeda found a 0.7°C average advantage.⁸ This difference may reflect our use of forced air warming whereas Ikeda did not use FAW. Also, Ikeda used a larger dose of propofol, which might cause more vasodilation and thus more redistribution hypothermia. Sun found 64% of 58,814 patients had a temperature $< 36^\circ\text{C}$ after 45 minutes, close to the 60% in group PROP; 29% were $< 35.5^\circ\text{C}$, close to the 22% in our group PROP.⁶ The similarity of these percentages is relevant only if the vast majority of Sun's cases were induced with intravenous propofol, which we presume to be the case. The differences may be due in part to Sun's patients having a higher mean age than our group PROP.

Twenty years ago, Ikeda et al found that inhalation inductions reduced redistribution hypothermia compared to IV propofol inductions.⁸ This study was done at a time when the concept of redistribution hypothermia was in development and so focused, and the adverse effects of hypothermia were not as well appreciated as they are currently. In addition, Ikeda studied 10 patients in each group, not enough to justify a change in national practice. The use of inhalation inductions to reduce redistribution hypothermia was not widely adopted. This study expanded on Ikeda's work by enlarging similar study groups and studying additional comparison groups. Replication of results is necessary if there is to be acceptance in the medical community, and it guards against incorrect conclusions and fraudulent publication.

In this randomized post-test only design, patients were randomly assigned separately within the age 18 to 55 and the >55 age groups. Only 1 or 2 randomly assigned patients in each group of 51 or 52 were not analyzed (Figure 1 legend). Of these 9 patients, in seven there were no post-induction temperature measurements as the patients were withdrawn before T₁₅; in two patients, there was only one temperature measurement at T₁₅. The randomized design, the multivariable analysis, and the observed differences provide assurance that our conclusions are valid.

Ikeda et al concluded that even a short period of vasodilation can result in meaningful redistribution hypothermia.⁸ Our study showed that a prior bolus dose of phenylephrine opposed enough of the propofol induced vasodilation to substantially reduce the amount of redistribution hypothermia. The phenylephrine was given about 10 seconds before the propofol to oppose vasodilation. Whether the phenylephrine would be as effective if given after the propofol is not known, since 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.

This study was designed to closely replicate common clinical practice. Many practitioners bolus propofol without depth of anesthesia monitoring. It would be unethical not to use FAW. The bolus doses of phenylephrine and midazolam were not weight based. Because the impact of these factors did not appear to be systematic, the large size of the comparison groups likely averaged out any nonsystematic differences between groups. The large outcome differences between comparison groups made it unlikely the major study conclusions were affected by these factors.

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. We did not control for "depth of anesthesia". A given dose of an anesthetic may induce varying depths in different patients; this could have contributed to the variability of patient responses within each group. Because the different groups received different anesthetic inductions, the average anesthetic depth could differ between groups; this may contribute to the thermal differences found between groups. Kazama et al found patients can be induced with a reduced total dose of propofol and with less hypotension when diluted propofol was administered as an

infusion.¹⁷ It remains to be demonstrated that Kazama's technique would result in less redistribution hypothermia.

Pre-warming has been shown to improve outcomes (decreased blood loss, transfusion requirement, and infection rate). Unfortunately, despite recommendations, prewarming is not universally used. However, even if the post induction core temperatures are similar between patients who were prewarmed and those who had an alternative induction, we cannot yet infer that using one of the three alternative induction techniques will result in the same beneficial clinical outcomes. Inhalation inductions and phenylephrine/propofol inductions reduce redistribution hypothermia because there is less vasodilation, pre-warming because the periphery and skin are warmer. Pre-warming adds heat content to the body; inhalation inductions and prophylactic phenylephrine do not. After induction, even if the core temperatures are similar, the peripheral and/or skin heat content in pre-warmed patients is certainly higher than those who received inhalation inductions or prophylactic phenylephrine. Since the periphery needs to be warmed before FAW raises core temperature, we hypothesize that pre-warmed patients will begin to rewarm more rapidly with initiation of FAW than patients who were not pre-warmed.

Techniques that can reduce redistribution hypothermia now include prewarming¹⁸⁻²², ketamine²³, etomidate²⁴, phenylephrine infusions²⁵, amino acid infusions²⁶, fructose²⁷, inhalation inductions, and bolus phenylephrine prior to propofol. None of these techniques solve the hypothermia problem fully. Combinations of these techniques (e.g., prewarming followed by inhalation induction, reducing the propofol dose by substituting an analgesic dose of ketamine, prophylactic bolus phenylephrine during inhalation induction) have the potential to result in additional thermal benefit, but require study. Our study protocol only permitted rescue phenylephrine (and not prophylactic) administration during inhalation inductions. It is plausible that a blended inhalation/propofol induction using a reduced dose of propofol also may have thermal (and hemodynamic) benefit.

Nasal temperature monitoring can be used with patients having an LMA; thus, the same measurement technique was used for all of our study patients. We used nasal temperature as a surrogate for core temperature measurement in this study since previous work has shown a close agreement between the nasal technique used in this study and distal esophageal temperature measurements.²⁸

The inhalation inductions were performed gradually without a primed circuit for two reasons. First, apnea is unlikely to occur. Using this induction technique, apnea never occurred in any of our 200 inhalation patients. Second, the gradual increasing of anesthetic depth likely contributes to hemodynamic stability, one of the potential benefits of inhalation inductions. A previous study concluded that inhalation inductions were more hemodynamically stable than IV propofol inductions.²⁹ Our study did not directly compare the hemodynamic stability between inhalation and intravenous inductions. However, we found no hypotension (systolic BP <85 mm Hg) in any patient who received an inhalation induction. Hypotension can occur rapidly with intravenous propofol inductions. Any changes in blood pressure with inhalation inductions would usually be more gradual and could be addressed earlier, or prophylactically, before there is clinically important hypotension. Retrospective studies have found that adverse outcomes

are associated with even short periods of hypotension, but not hypertension.^{30,31} Maheshwari et al recently documented that a substantial fraction of all hypotension occurs before surgical incision as a result of anesthetic management and this hypotension is associated with postoperative kidney injury.³² Although our results hint at a hemodynamic benefit of these alternative induction techniques, the study design focused on temperature and do not allow for any such conclusions. Studies investigating the hemodynamic benefits are now warranted.

In Group Phnl/PROP, we found 160 mcg phenylephrine to be an effective dose in most patients, but it may not be optimal. Small percentages of patients had a post-induction systolic blood pressure either <85 mm Hg or >180 mm Hg. A yet to be determined optimal phenylephrine dose (e.g., weight based) that further minimizes hypo- and hypertension events and still maintains the thermal benefit may differ from the dose we used in this study.

Practitioners may avoid inhalation inductions because of time delay or because of patient dislike. Muzi et al demonstrated that the speed of inhalation induction approached that of an intravenous induction using a primed circuit.³³ When patients were offered a choice, 50% chose an inhalation induction, 33% chose IV induction, and 17% were undecided.³⁴ Unfortunately, because of personnel limitations, we could not record and compare induction times.

In the second temperature phase, clinicians expect obese patients to be more resistant to temperature changes as it takes more heat gain or loss to change the mean temperature of a more massive patient. However, there are different considerations during the redistribution hypothermia phase. In the multivariable analysis, neither BMI nor sex were associated with the degree of redistribution hypothermia. This suggests the differences of BMI and sex between groups are not the reasons for the observed differences between groups. It appears all patients, obese and nonobese, are at risk for redistribution hypothermia. Many obese patients have substantial muscle mass in their periphery to move their heavy body parts. Adipose tissue gets relatively little blood flow; this may prevent meaningful temperature buffering during the redistribution hypothermia phase. As examples, four patients who had BMIs of 42.0, 37.7, 37.7, and 39.2 kg/m² had a lowest temperature of 35.4°C, 35.2°C, 35.5°C, and 35.6°C respectively, the lowest or near lowest in their group. Obese patients are susceptible to RH.

Older patients are believed to be more prone to hypothermia than younger patients.¹¹⁻¹³ Our results suggest inhalation inductions are effective in reducing redistribution hypothermia in older patients. Although we found numerically lower mean temperatures in the older age inhalation groups compared to the younger inhalation groups, these differences were not statistically significant. (This study was not designed to have the statistical power to find such a difference in this secondary outcome.) In the comparisons between older patients who had an inhalation induction and young patients who had a propofol alone induction, the older patients had statistically significant higher mean core temperatures and a smaller chance of having a temperature <36.0°C in the first hour. Sedation with midazolam can lead to a decrease in core temperature.³⁵ Some elderly patients received a reduced dose of midazolam possibly resulting in higher mean core temperatures in those groups. Since these exploratory

comparisons were non-randomized, these results involving patients aged >55 years need to be further examined in future studies.

Without patient warming, temperature decreases can continue for 3 hours.³⁶ With the prompt initiation of forced air warming, we found that the major effect of redistribution hypothermia occurred during the first 15 minutes after induction in most patients. After 30 minutes, the warming effect of FAW countered or exceeded that of redistribution hypothermia in the majority of patients (Figure 2).

Conclusions

This study demonstrates the thermal benefits of inhalation inductions and prophylactic bolus phenylephrine administration in adults. This study should prompt a reconsideration of our anesthetic practice, particularly since prewarming is not universally used. Inhalation inductions with sevoflurane are safe, quick and easy to perform in most adults, and may provide more hemodynamic stability. However, definitive randomized controlled studies are needed to confirm that such changes in induction technique will result in improved clinical outcomes. In addition, financial benefits may accrue. In the United States, the new MACRA temperature target (35.5°C) may now be easier to achieve.¹⁰ Avoidance of unpleasant side effects (e.g., shivering) may result in less patient dissatisfaction. Reducing hypothermia associated complications will reduce cost. Appendix 1 presents situations where a reduction in redistribution hypothermia may be particularly helpful. Rarely does one come across a partial solution that is so easy, effective, and inexpensive to implement. Because these techniques do not fully solve the hyperthermia problem should not be a reason not to use them.

Abbreviations

AAA – abdominal aortic aneurysm

ASA – American Society of Anesthesiologists

BMI – body mass index

BP – blood pressure

C – centigrade

CDC – Centers for Disease Control

CHIP – Children’s Health Insurance Program

CI – confidence interval

D&C – dilation and curettage

EBUS - endobronchial ultrasound

ECC - Endocervical curettage

FAW – forced air warming

Hg - mercury

INH/50 – study group aged 18-55 induced with 50% oxygen and 50% nitrous oxide

INH/50>55 - study group aged >55 induced with 50% oxygen and 50% nitrous oxide

INH/100 - study group aged 18-55 induced with 100% oxygen

INH/100>55 – study group aged >55 induced with 100% oxygen

IV - intravenous

kg - kilogram

LEEP - loop endocervical excision procedure

LMA – laryngeal mask airway

LPM – liters per minute

m – meter

MACRA - Medicare Access and CHIP Reauthorization Act

mcg – microgram

mg – milligram

mL - milliliter

mm – millimeter

MN – Minnesota

N₂O – nitrous oxide

O₂ – oxygen

Phnl/PROP - study group aged 18-55 induced with 160 mcg phenylephrine followed by 2.2

mg/kg IV propofol

PROP – study group aged 18-55 induced with 2.2 mg/kg IV propofol

RFA – radiofrequency ablation

SD – standard deviation

T_x – time x minutes after the start of anesthetic induction

VAC - Vacuum Assisted Closure

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 a repository. (I am new to this process and it may take me a little while to accomplish this, but I think clinical.trials.gov may be most suitable. I will contact your help desk within a week.)

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. Will respond to reviewers during revision process.

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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None

Author information

In 2009, in preparing for my Open-Mind editorial in Anesthesia & Analgesia, I came across Ikeda's 1999 study on inhalation inductions. Without talking about it to anyone, I started performing inhalation inductions. One month later, a PACU nurse, who did not know I changed my technique, asked me if I was doing anything differently since my patients were coming out warmer. This effect was noticed by a blinded impartial observer! I continued with this technique for one year and convinced myself the effect was real. Since intravenous inductions, not inhalation inductions, are the preferred anesthetic induction technique in adults, I tried writing a letter to the editor to inform the public but was twice told 20 patients was not enough to justify a change in anesthetic practice. They suggested that I performed a prospective controlled study. This study accomplished that. By necessity, it largely repeated what Ikeda did, but it has more power and studied additional groups. The similarity of results between Ikeda's study and this one is necessary if there is to acceptance of these findings.

I have been using inhalation inductions as my technique of choice when there is no contraindication. It would probably be difficult to find a non-pediatric anesthesiologist who has performed as many inhalation inductions in adults as I have. Besides from the thermal benefits which are documented in this study, I believe there are other benefits to inhalation inductions.

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Tables

Table 1 - Study groups

| Group | Age (years) | Induction technique |
|--------------|----------------|---|
| INH/100 A | 18 to 55 | Inhalation: 8% sevoflurane in 100% oxygen |
| INH/50 B | 18 to 55 | Inhalation: 8% sevoflurane in 50% oxygen and 50% nitrous oxide* |
| PROP C | 18 to 55 | Intravenous: 2.2 mg Propofol |

Phyl/PROP 18 to 55 Intravenous: 2.2 mg propofol preceded by 160 mcg phenylephrine

D

INH/100>55 >55 Inhalation: 8% sevoflurane in 100% oxygen**

AA

INH/50>55 >55 Inhalation: 8% sevoflurane in 50% oxygen and 50% nitrous oxide

BB

* 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.¹⁴ 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.

** Intravenous inductions were not studied in patients over 55 years. In such patients, the dose of propofol would need to be reduced by varying amounts (difficult to determine objectively). The possible inaccuracies in dose would make such an analysis unreliable.

Table 2 - Inclusion and exclusion criteria

INCLUSION CRITERIA

Age 18 years or greater

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

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 (2 if over 55 years of age) 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

| Group | INH/100 | INH/50 | PROP | Phnl/PROP | INH/100>55 | INH/50>55 |
|--------------------|-------------|------------|-------------|-----------|------------|------------|
| Age (years) | | | | | | |
| Mean (SD) | 42.8 (10.1) | 43.0 (8.6) | 39.0 (11.2) | 40.6(9.1) | 68.2 (8.4) | 66.2 (7.4) |
| Range | 22 to 55 | 26 to 55 | 18 to 55 | 20 to 55 | 56 to 88 | 56 to 85 |
| Sex | | | | | | |
| Male n (%) | 20 (40) | 31 (62) | 20 (40) | 21 (42) | 32 (64) | 26 (52) |
| ASA classification | | | | | | |
| 1 n (%) | 1 (2) | 3 (6) | 10 (20) | 2 (4) | 0 (0) | 0 (0) |
| 2 n (%) | 23 (46) | 23 (46) | 29 (58) | 33 (66) | 10 (20) | 10 (20) |

| | | | | | | | |
|--|-----------|--------------|--------------|--------------|--------------|--------------|--------------|
| 3 | n (%) | 16 (52) | 24 (48) | 11 (22) | 15 (30) | 40 (80) | 40 (80) |
| BMI (kg/m ²) | | | | | | | |
| | Mean (SD) | 31.9 (7.5) | 31.2 (6.7) | 26.8 (5.6) | 29.9 (6.4) | 28.9 (6.5) | 29.3 (6.3) |
| | Range | 21.7 to 48.9 | 18.9 to 44.2 | 17.2 to 43.0 | 15.1 to 44.4 | 20.2 to 57.5 | 18.2 to 43.0 |
| Preoperative screening temperature (°C) | | | | | | | |
| | Mean (SD) | 36.8 (0.3) | 36.8 (0.3) | 36.8 (0.3) | 36.70 (0.3) | 36.8 (0.3) | 36.8 (0.3) |
| Use of upper body forced air warming (FAW) blanket (remaining patients used lower body FAW) | | | | | | | |
| | n | 32 | 39 | 29 | 30 | 25 | 29 |
| | (%) | (64) | (78) | (58) | (60) | (50) | (58) |
| Time from T ₀ until FAW turned on, (minutes) | | | | | | | |
| | Mean (SD) | 16.4 (7.0) | 14.7 (7.0) | 15.9 (7.9) | 17.1 (7.7) | 17.4 (7.9) | 16.6 (8.1) |
| | Range | 5 to 45 | 4 to 45 | 4 to 44 | 6 to 40 | 5 to 42 | 4 to 43 |

Table 4 - List of surgeries

| Procedure | Groups* having at least one patient having procedure | | | | | |
|---------------------------|--|---|---|---|----|----|
| UROLOGIC | | | | | | |
| Cystoscopic surgery | A | B | C | D | AA | BB |
| Penile procedures | A | B | C | | AA | BB |
| Suprapubic tube placement | A | | | | AA | |

Scrotal procedures A C D BB

Urethroplasty B C D BB

ORTHOPEDIC

Lower extremity orthopedics A B C D AA BB

Upper extremity orthopedics A B C D AA

Anterior cervical discectomy and fusion D BB

GYNECOLOGIC

Vulvoplasty or excision of lesion A B

D&C, hysteroscopy A B C D

Loop endocervical excision procedure (LEEP) A B

Endocervical curettage (ECC) A B

Hysterectomy A B D

Myomectomy B C D

VASCULAR

Dialysis access related procedures A B C D AA BB

Lower extremity vascular - open procedures B AA BB

RFA and/or Lower extremity phlebectomies A B C

Endovascular AAA AA BB

Lower extremity amputations A B AA BB

DENTAL/ENT A C D AA BB

INH/100 minus PROP

| | | | | |
|-----------------|--------------|--------------|--------------|--------------|
| Difference (°C) | 0.46 | 0.46 | 0.47 | 0.49 |
| 95% CI | 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 | 0.31 to 0.64 | 0.36 to 0.69 | 0.31 to 0.69 | 0.28 to 0.79 |

Phnl/PROP minus PROP

| | | | | |
|-----------------|--------------|--------------|--------------|--------------|
| Difference (°C) | 0.39 | 0.41 | 0.45 | 0.47** |
| 95% CI | 0.24 to 0.54 | 0.25 to 0.57 | 0.27 to 0.63 | 0.25 to 0.70 |

*P≤0.001 for all above comparisons

**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.

Table 6 Comparison the three alternative induction groups to the standard propofol alone group having temperatures <36°C and ≤35.5°C in the first hour in patients aged 18 to 55

One or more temperatures <36°C in first hour

| Group | INH/100 | INH/50 | PROP | PhnlPROP |
|-------|---------|---------|----------|----------|
| n (%) | 8 (16%) | 8 (16%) | 30 (60%) | 8 (16%) |

| Comparison groups | Difference | 95% CI | p value |
|-------------------|---------------------|--------|---------|
| | (percentage points) | | |

| | | | |
|----------------------|-----|------------|---------|
| PROP minus INH/100 | 44% | 27% to 61% | <0.0001 |
| PROP minus INH/50 | 44% | 27% to 61% | <0.0001 |
| PROP minus Phnl/PROP | 44% | 27% to 61% | <0.0001 |

One or more temperatures $\leq 35.5^{\circ}\text{C}$ in first hour

| Group | INH/100 | INH/50 | PROP | PhnlPROP |
|-------|---------|--------|----------|----------|
| n (%) | 4 (8%) | 2 (4%) | 11 (22%) | 1 (2%) |

| Comparison groups | Difference | 95% CI | p value |
|----------------------|---------------------|-------------|---------|
| | (percentage points) | | |
| PROP minus INH/100 | 14% | 0.3% to 28% | 0.09*** |
| PROP minus INH/50 | 18% | 5% to 31% | 0.015 |
| PROP minus Phnl/PROP | 20% | 8% to 32% | 0.004 |

***The 95% CIs are asymptotic (approximate); the p values are exact. In this one case when the p value and 95% CI yield different conclusions, the exact p value should be used.

Table 7 Comparisons of mean core temperature ($^{\circ}\text{C}$) at each time point between patients aged >55 and patients aged 18 to 55

| Comparison groups | T ₁₅ | T ₃₀ | T ₄₅ | T ₆₀ |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| INH/100>55 minus PROP* | | | | |
| Difference ($^{\circ}\text{C}$) | 0.37 | 0.36 | 0.29 | 0.30 |
| 95% CI | 0.20 to 0.54 | 0.18 to 0.53 | 0.09 to 0.50 | 0.06 to 0.55 |
| p value | <0.0001 | 0.0001 | <0.005 | 0.02 |

INH/50>55 minus PROP*

| | | | | |
|-----------------|--------------|--------------|--------------|--------------|
| Difference (°C) | 0.44 | 0.43 | 0.41 | 0.41 |
| 95% CI | 0.26 to 0.63 | 0.24 to 0.62 | 0.19 to 0.63 | 0.14 to 0.68 |
| p value | <0.0001 | 0.001 | 0.0004 | 0.003 |

INH/100* minus INH/100>55

| | | | | |
|-----------------|---------------|---------------|---------------|---------------|
| Difference (°C) | 0.09 | 0.11 | 0.18 | 0.18 |
| 95% CI | -0.10 to 0.27 | -0.09 to 0.30 | -0.05 to 0.40 | -0.08 to 0.45 |
| p value | 0.37 | 0.28 | 0.12 | 0.17 |

INH/50* minus INH/50>55

| | | | | |
|-----------------|---------------|---------------|---------------|---------------|
| Difference (°C) | 0.03 | 0.09 | 0.09 | 0.13 |
| 95% CI | -0.16 to 0.22 | -0.10 to 0.29 | -0.13 to 0.31 | -0.13 to 0.38 |
| p value | 0.76 | 0.35 | 0.41 | 0.32 |

*These groups were comprised of patients age 18 to 55 years.

Table 8 Comparisons between the percentages of patients aged >55 and patients aged 18 to 55 having temperatures <36°C and ≤35.5°C in the first hour

One or more temperatures <36°C in first hour

| Group | INH/100 | INH/100>55 | INH/50 | INH/50>55 | PROP |
|-------|---------|------------|---------|-----------|----------|
| n (%) | 8 (16%) | 14 (28%) | 8 (16%) | 14 (28%) | 30 (60%) |

| Comparison groups | Difference | 95% CI | p value |
|-------------------|------------|--------|---------|
|-------------------|------------|--------|---------|

(percentage points)

| | | | |
|---------------------------|-----|------------|-------|
| PROP* minus INH/100>55 | 32% | 14% to 50% | 0.002 |
| PROP* minus INH/50>55 | 32% | 14% to 50% | 0.002 |
| INH/100>55 minus INH/100* | 12% | -4% to 28% | 0.23 |
| INH/50>55 minus INH/50* | 12% | -4% to 28% | 0.23 |

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One or more temperatures $\leq 35.5^{\circ}\text{C}$ in first hour

| Group | INH/100 | INH/100>55 | INH/50 | INH/50>55 | PROP |
|-------|---------|------------|--------|-----------|----------|
| n (%) | 4 (8%) | 5 (10%) | 2 (4%) | 3 (6%) | 11 (22%) |

| Comparison groups | Difference | 95% CI | p value |
|-------------------|------------|--------|---------|
|-------------------|------------|--------|---------|

(percentage points)

| | | | |
|---------------------------|-----|------------|------|
| PROP* minus INH/100>55 | 12% | -2% to 26% | 0.17 |
| PROP* minus INH/50>55 | 16% | 3% to 29% | 0.04 |
| INH/100>55 minus INH/100* | 2% | -9% to 13% | 1.0 |
| INH/50>55 minus INH/50* | 2% | -7% to 11% | 1.0 |

*These groups were comprised of patients age 18 to 55 years.

Figures

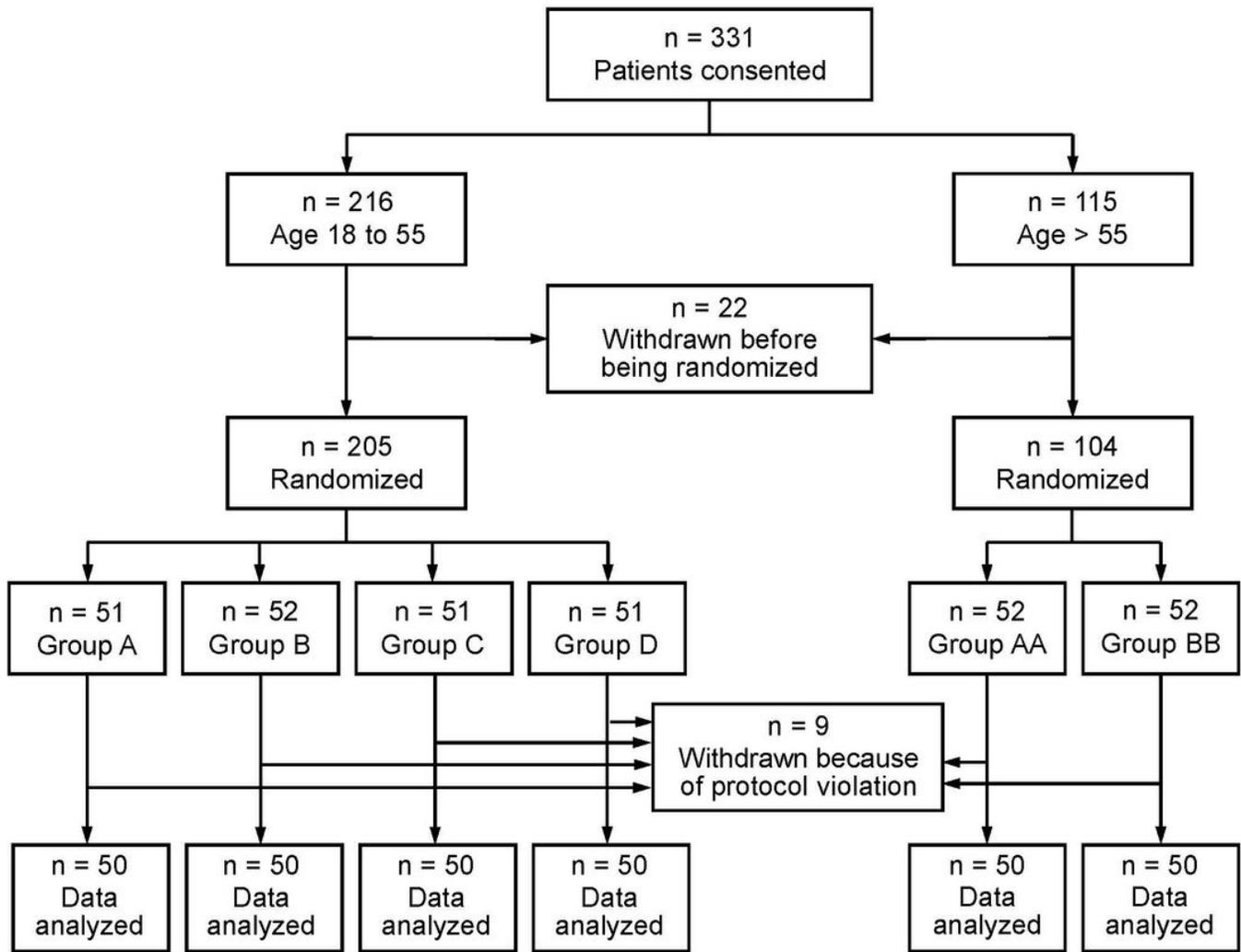


Figure 1

Consort Diagram. Legend/Caption of figure 1: Twenty-two patients consented but were never randomized and not studied: 20: 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. Nine patients were induced and then withdrawn from analysis* because of protocol violations: 1: Airway difficulty during induction 1: Additional propofol required 1: Surgery ended before 30 minutes 2: Patients received more than 300 mL unwarmed IV fluid 3: Forced air warming malfunctions 1: Cold bladder irrigation *In seven patients, there were no post-induction temperature measurements as the patients were withdrawn before T15. In two patients, there was only one temperature measurement at T15.

**Mean Temperature \pm SD and Number (n)
in Each Group at Each Time Point ($^{\circ}$ C)**

| | T15 | T30 | T45 | T60 |
|-----------------------------|--------------------------|--------------------------|--------------------------|--------------------------|
| INH/100 —■— | 36.42 \pm 0.49 (50) | 36.41 \pm 0.49 (50) | 36.47 \pm 0.53 (37) | 36.52 \pm 0.56 (27) |
| INH/50 —●— | 36.44 \pm 0.44 (50) | 36.48 \pm 0.44 (50) | 36.50 \pm 0.48 (41) | 36.57 \pm 0.42 (28) |
| PROP - -△- - | 35.96 \pm 0.40 (50) | 35.95 \pm 0.41 (50) | 36.00 \pm 0.45 (43) | 36.03 \pm 0.53 (32) |
| Phnl/PROP - -▲- - | 36.35 \pm 0.38 (50) | 36.36 \pm 0.40 (50) | 36.45 \pm 0.40 (45) | 36.51 \pm 0.40 (40) |
| INH/100 > 55□..... | 36.34 \pm 0.46 (50) | 36.31 \pm 0.48 (50) | 36.29 \pm 0.50 (46) | 36.34 \pm 0.51 (39) |
| INH/50 > 55 - -○- - | 36.41 \pm 0.52 (50) | 36.38 \pm 0.53 (50) | 36.41 \pm 0.57 (43) | 36.44 \pm 0.55 (34) |

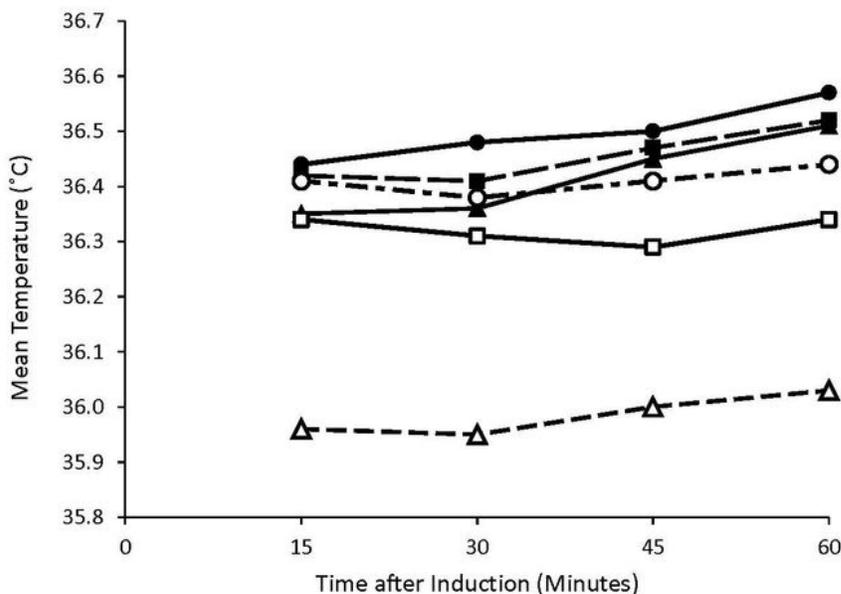


Figure 2

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 continued to decrease lessened (40% to 16.4% to 14.5% respectively) while the percentage of patients whose temperature increased rose (34.7% to 46.7% to 55.5% respectively). The remaining patients had no interval temperature changes. This result is reflected in the positive slopes for groups INH/100, INH/50, and Phnl/PROP from T30 to T45 and T45 to

T60. Most of the interval temperature differences were small. In all groups combined, there was either no temperature change or a 0.1°C change in 91% of the 15 minute intervals.