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Prewarming Followed by Active Warming is Superior to Passive Warming in Preventing Hypothermia for Short Procedures in Adult Rats (*Rattus norvegicus*) Under Isoflurane Anesthesia

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General anesthesia is a common procedure in laboratory rats; however, it impairs thermoregulation, rapidly leading to hypothermia as warm core blood is distributed to the cooler periphery. The protective strategy of prewarming before the onset of anesthesia delays hypothermia, but only for a short period. This prospective, randomized, cross-over, experimental study in adult male and female SD rats (n = 8) was designed to compare passive (fleece blanket) and active (temperature controlled heating pad) warming. Initial treatment order was randomized, with a cross-over after a minimum 5 d washout period. Both groups underwent a period of prewarming in a warming box to increase core temperature by 1% (median 0.4 °C). At completion of prewarming, general anesthesia was induced and maintained for 30 min with isoflurane carried in oxygen. Core temperature was monitored for a further 30 min after anesthesia. Active warming resulted in higher core temperatures during anesthesia. During passive warming, hypothermia occurred after approximately 30 min of anesthesia and continued into recovery. In contrast, active warming prevented hypothermia. Prewarming followed by passive warming delayed hypothermia for approximately 30 min, but active warming was more effective at maintaining normothermia both during and after general anesthesia.

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Core body temperature is normally tightly regulated in conscious animals through a variety of autonomic responses and behaviors.[12,29] Receiving afferent inputs from temperature receptors widely distributed in the body, the hypothalamus mediates autonomic control, with effector responses altering cutaneous vascular tone to vary blood flow (and consequently the transfer of heat) through arteriovenous shunts by several orders of magnitude.[12] Under general anesthesia, these regulatory mechanisms are disrupted, and as a result, the hypothalamic threshold range (± 0.2 to 0.4 °C; defined as the temperature range that does not trigger a thermoregulatory autonomic response) increases 20 fold (4 to 8 °C) before an autonomic response is activated.[10,13,41] Consequently, hypothermia is a common complication of general anesthesia and a challenge for anesthetists.[24,25,27,40]

The most important promoter of hypothermia during anesthesia is broadening of the hypothalamic threshold range, which allows warm core blood to redistribute to the periphery and subsequently lose heat to the environment.[3,4,20,32,41] Redistribution accounts for 80% of the drop in core temperature that follows the induction of general anesthesia.[8,20] Once hypothermia is established, reversal can be difficult.[32] Because relatively small reductions in core temperature (as little as 1 °C in humans) are associated with important adverse effects (surgical site infections, altered drug pharmacokinetics, delayed recovery from anesthesia, prolonged hospital stay), the prevention of hypothermia is an important goal during anesthesia.[14,16,17,33] Prolonged recovery from anesthesia occurs in hypothermic dogs and rodents.[6,23,31]

To minimize thermoregulatory dysfunction caused by general anesthesia, instituting protective warming strategies before initiation of anesthesia has been shown to reduce heat redistribution.[5,11,37,39] The strategy of warming patients to minimize the temperature gradient between the core and the periphery has been successfully implemented in humans.[5,11,37,39] Prewarming prolongs the duration of normothermia after the induction of general anesthesia by limiting the initial redistribution of heat that occurs during anesthesia.[5,11,37,39] A similar strategy was unsuccessful in dogs,[1,26] but has been successfully employed in rats.[28,31] In rats, the duration of effect of prewarming was relatively short (approximately 15 min) when used alone, and the contribution of active compared with passive warming in maintaining normothermia after prewarming has not been investigated.[28,31]

This study was designed to explore the effectiveness of different warming strategies after a period of prewarming in rats. We hypothesized that prewarming to a target 1% increase in core temperature, followed by passive warming (fleece blanket), would prevent hypothermia during 30 min of general anesthesia.

Materials and Methods

Animals. Female (n = 5) and male (n = 3) CD Sprague–Dawley rats aged (28 wk [14 to 28 wk]; median [range]) and

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body mass of 408g (362 to 618g) were purchased from a commercial supplier (Charles River Laboratories, Senneville, QC, Canada).

Ethics statement. The experimental protocol was approved by the institutional animal care and use committee of the Université de Montréal (18-Rech-1947), which follows the requirements of the Canadian Council on Animal Care.

Rats were acclimatized to both the experimenter (MR) and environment over a 7-d period that included daily handling and exposure to the warming chamber. Rats were considered habituated when they readily accepted a treat offered by hand. Rats were pair-housed in a plastic cage (45 [l] x 24 [w] x 20 [h] cm) with bedding of wood chips and shredded paper. A plastic tube and a polyurethane toy were included for enrichment. Environmental conditions were controlled to provide a 14/10 h light:dark cycle (lights on at 0600), humidity of 35% to 40%), and temperature of 22 °C. Rats were fed a standard rodent diet (Rodent laboratory chow 5075, Charles River Breeding Laboratories, St-Constant, Quebec, Canada), and tap water was offered ad libitum. In addition to standard diet, 3 types of small palatable treats were offered *ad hoc* (Supreme Mini-Treats, Very berry flavor, Bio-Serv, Flemington, NJ 08822, USA; Veggie-Bites, Bio-Serv, Flemington, NJ 08822, USA; Fruit Crunchies, Bio-Serv, Flemington, NJ 08822).

A sample size estimate of 8 animals was based on an α of 0.05 and power of 80% to identify a mean difference in core body temperature between treatment groups of 1 °C with a standard deviation of 0.5 °C. This was based, in part, on published data.[31]

Telemetric temperature capsule implantation. Rats were instrumented with a telemetry capsule (Anipill temperature sensor; Aniview system, Bodycap, Hérouville-Saint-Clair, France) implanted in the peritoneal cavity to monitor core temperature as part of a related study.[28] Capsule implantation was performed 10 wk before the experiments began.

Intraoperative temperature management. A prospective, randomized, cross-over experimental study was designed with 2 groups: passive and active warming. Before beginning the study, rats were randomized to the first treatment with the cross-over taking place after a minimum 5 d washout period. The study design and presence of a single experimenter precluded blinding to treatment assignment. Exclusion criteria during the experiment were a core temperature less than 27 °C or greater than 41 °C, the presence of cutaneous thermal injuries, and any weight loss equivalent to 2% of body weight or more over the 5 d after. Testing was performed between 0900 and 1700.

We established a baseline core temperature for each animal by calculating the mean of core temperatures sampled every 300 s between 0800 to 1800 on the day before the experiment. To facilitate comparisons between treatment groups, individual core temperatures were pooled from all animals and a hypothermic threshold calculated (mean core temperature minus 2 standard deviations).

The first part of the experiment was identical for both treatment groups and consisted of prewarming and induction of general anesthesia. The chamber used for prewarming and anesthetic induction (25.7 [l] x 11 [w] x 10.7 [h] cm; Small box, Harvard apparatus, Holliston, MA) was preheated to a temperature of 32.6 ± 1.1 °C (measured with a calibrated infrared thermometer) using a purpose-built heating unit (Vetronic Services, England).[28] To achieve prewarming, a single rat was placed in the chamber, where it remained its core temperature increased to 1% above the value recorded before entry into the chamber. Once the prewarming target was attained, isoflurane was started (5% isoflurane on the vaporizer dial carried in 1L/min oxygen) and general anesthesia was induced.

Passive warming group. After loss of the righting reflex, rats were removed from the induction chamber, placed on a thin pad composed of synthetic absorbent material (17" x 24", Ultra Blok, A.M.G. Medical Montreal, QC) and covered with a fleece blanket (Microfleece throw, 50 in. × 60 in, Mainstays, Wal-Mart, Bentonville, AR). General anesthesia was maintained for a further 30 min using a nose cone (isoflurane vaporizer set at 1.75%, 1L/min oxygen), after which isoflurane was discontinued. After the rats recovered sternal recumbency, they were returned individually to a cage containing the same bedding materials as the home cage.

Active intraoperative temperature management group. After loss of the righting reflex, each rat was removed from the chamber, and anesthesia continued as described above. Rats in this group were placed on a heating pad that was set to 37 °C (16 × 38 cm; Stoelting Rodent Warmer with Cage Heating Pad, Stoelting Corporation, Wood Dale, IL). Rats were always placed in the same area of the heating pad.[42] After the rats recovered sternal recumbency, they were returned individually to a cage containing the same bedding materials as the home cage.

Temperature monitoring. Core temperature was monitored (sampling frequency, 150 s) continuously from the time of the animal's entry into the warming chamber until 30 min after isoflurane was discontinued. Rectal temperature was measured every 5 min during the 30 min of general anesthesia by using a thermometer (Physio Logic Accuflex Pro, Model 16 to 639; AMG Medical, Montreal, QC, Canada) inserted to a standardized depth of 6 cm. Thermometer accuracy was checked using a water bath and compared with a calibrated thermometer. Skin temperature, measured at the lateral surface of the elbow and stifle (right thoracic and pelvic limb), was recorded immediately before entry and after removal from the warming chamber. Rectal temperature, which remains a commonly used proxy for core temperature, was compared to the core temperature measured by telemetry. Skin temperatures were recorded to assess the effects of prewarming on reducing the temperature gradient between the periphery and core.

Active warming systems evaluation. As part of a separate audit, every active warming blanket available within our facilities was evaluated in terms of surface temperature output ($n = 21$). Warming blankets were set at 38 °C, a temperature marked on the control dial and were allowed to heat for 30 min before measurements were taken with a calibrated infrared thermometer. The entire length of the blanket was divided in 3 equal parts (top, middle, bottom). A total of 3 measures were taken from each of the parts to obtain a mean temperature for top, middle, and bottom sections.

Statistical analysis. Data were analyzed with commercial software (Prism 8.1.2, GraphPad Software, La Jolla, CA, and MedCalc Software 18.5, Ostend, Belgium). All data approximated a normal distribution according to the D'Agostino-Pearson Omnibus normality test. Time to hypothermia (based on the individually calculated hypothermia threshold) was assessed with a paired t test. The effectiveness of the 2 treatments was assessed by calculating the area under the curve. Two curves were defined for analysis: 1) start of anesthesia to end of anesthesia (time 0 to 30 mins) and 2) 30 min after the end of anesthesia (time 30 to 60 mins). Areas under the curves were compared between groups with a 1-way ANOVA (*posthoc* Tukey test). Comparisons between core and rectal temperatures were performed with a 2-way ANOVA of repeated measures and *posthoc* Bonferroni test. P values of < 0.05 were considered significant. Data are presented as mean ± SD in the text and mean ± SEM in the figures. Data supporting the results are available in an electronic repository (https://doi.org/10.7910/DVN/XKHR7N).

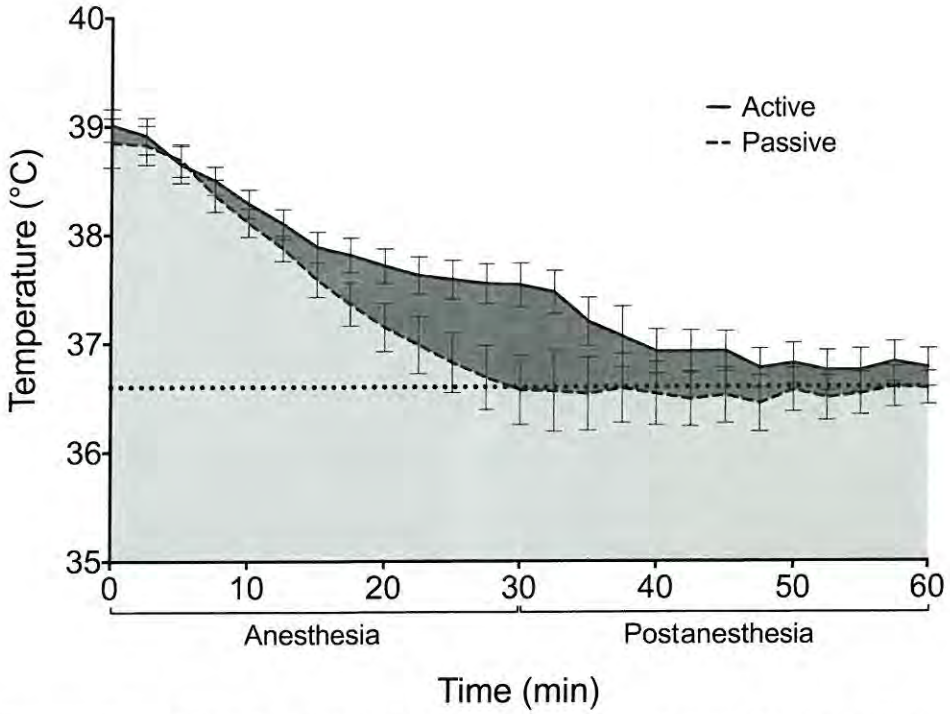

Figure 1. Area under the curve of core temperature changes in rats prewarmed to 1% above individual baseline temperature before induction of general anesthesia. Core temperature was recorded: 1) during 30 min of anesthesia (n = 8) and during 30 min of recovery (postanesthesia, n = 8). Time taken to reach hypothermia threshold (36.6 °C, horizontal dotted line) was 30 min in the passive group. Hypothermia did not occur in the active heating group. Data presented as mean ± SEM.

Results

None of the rats were excluded from the experiment (n = 8 per group). A transitory reduction in body weight occurred in 2 different animals; one rat lost 5% body weight after passive warming, and another lost 1% after active warming. The mean core temperature of all rats during baseline was 37.2 ± 0.3 °C with a derived hypothermia threshold of 36.6 °C (mean temperature – 2 SD). Prewarming increased core temperature to the targeted 1% over baseline (median; 0.4 °C, range; 0.4 to 0.5 °C). The time to achieve the 1% increase was 16.7 ± 4.3 min. Prewarming increased skin temperature by 4.9 ± 0.5 °C for the passive warming group and 5.1 ± 0.6 °C for the active warming group. The core body temperatures of all rats decreased after induction of general anesthesia (time 0 to 30 min, Figure 1).

Prewarming followed by active heating prevents hypothermia. Significant differences in the areas under the curve occurred between the 2 treatment groups during both the 30 min of general anesthesia and the 30 min recovery period. Core temperature was better maintained in the active heating group than the passive heating group both during anesthesia (P = 0.008 [95%CI 3.2 to 20.4]) and after anesthesia (P = 0.002 [95%CI 4.2 to 17.7]) anesthesia (Figure 1).

Heat distribution after prewarming and during general anesthesia. Prewarming raised both the core temperature and the peripheral (skin) temperature. This resulted in a smaller difference between core and rectal temperatures during the 30 min of anesthesia in the active warming group (Figure 2 A). In contrast, differences of up to 0.7 °C were recorded between sites in the passive warming group (Figure 2 B). These differences were smaller during the 30 min anesthesia period for the active warming group (Figure 2 A)

During the 30 min general anesthesia period for the active group, rectal and core temperature differed significantly at T10 (P = 0.002, 95% CI -0.55 to -0.10), T15 (P = 0.017, 95% CI -0.49 to -0.03) and T30 (P = 0.017, 95% CI -0.50 to -0.03). There were no significant differences at the other time points: T0 (P = 1.0, 95% CI -0.13 to 0.33), T5 (P = 0.057, 95% CI, -0.45 to 0.004), T20 (P = 0.13, 95% CI -0.43 to 0.03) and T25 (P = 0.057, 95% CI -0.45 to 0.004).

During the 30 min general anesthesia period for the passive group, rectal and core temperatures differed significantly at T5 (P < 0.0001, 95% CI -0.92 to -0.38), T10 (P < 0.0001, 95% CI -0.92 to -0.38), T15 (P = 0.0001, 95% CI -0.73 to -0.19) and T20 (P = 0.014, 95% CI -0.58 to -0.04). There were no significant differences at other times: T0 (P = 1, 95% CI -0.26 to 0.28), T25 (P = 0.12, 95% CI -0.51 to 0.03) and T30 (P = 0.67, 95% CI -0.43 to 0.11).

Active warming system evaluation. Despite being set at the same target temperature, major discrepancies were identified for all warming blankets. The most impressive difference was found between blanket no. 1 (bottom area) and no. 21 (middle area), the latter being 18.2 °C higher. Considerable differences were also found within individual blankets. For example, blanket no. 18 had a difference of 7.7 °C between the middle and top area (Table 1). The highest difference in surface temperature was identified between the different sections for all individual blankets, and results were pooled. This highlighted the areas were heterogeneous in their recorded surface temperature, with a pooled mean difference of 1.6 ± 1.5 °C (mean ± SD).

Discussion

This study had 3 main findings. First, prewarming to a targeted 1% increase over baseline core temperature was successfully achieved. Second, prewarming followed by active warming prevented hypothermia during general anesthesia. Third, prewarming followed by passive warming delayed the onset of hypothermia but did not prevent it from occurring during the recovery period.

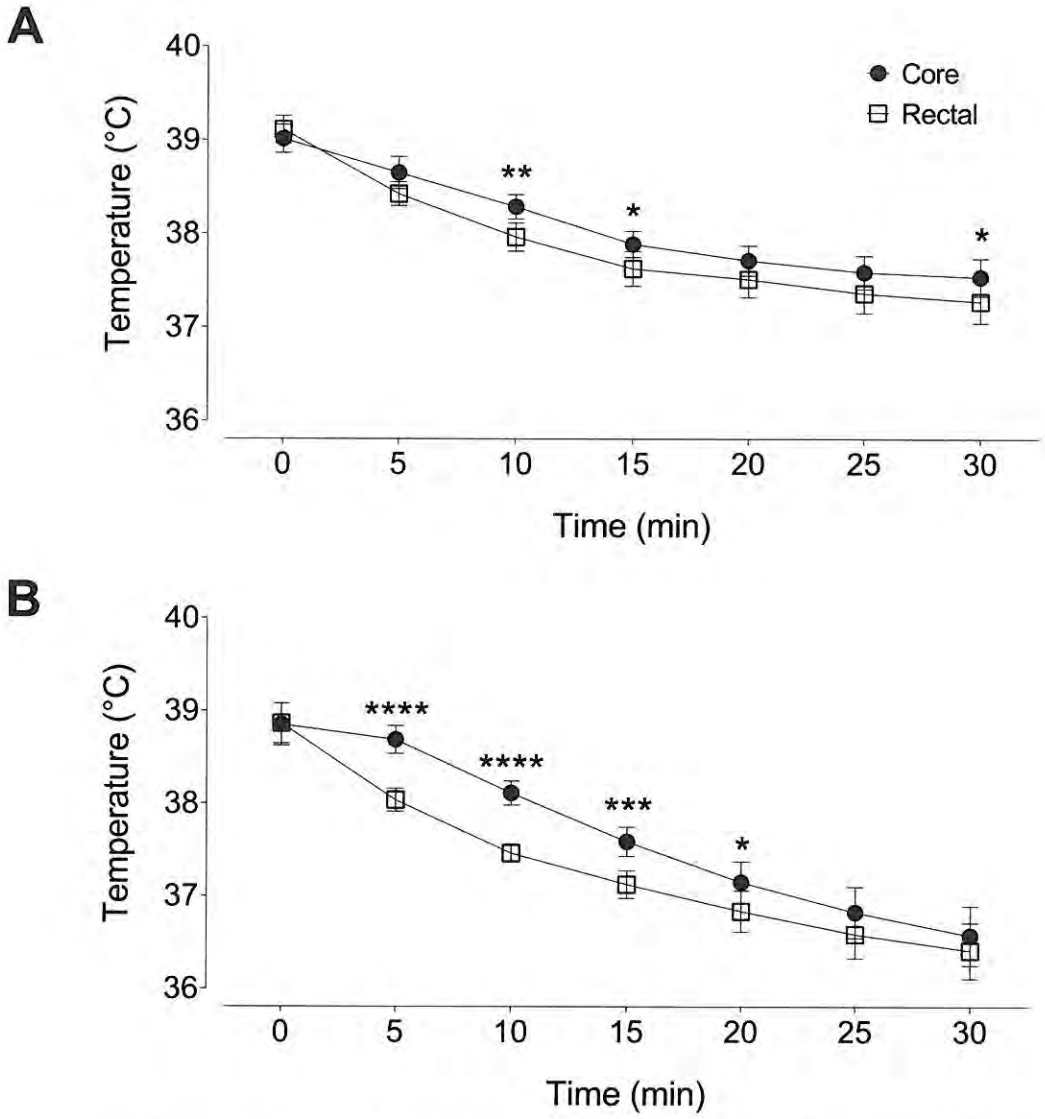

Figure 2. Core and rectal temperature profile under the 30 min general anesthesia period of Sprague–Dawley rats ($n = 8$). (A) Rats were subjected to active thermal support (heat pad) or (B) passive thermal support (fleece draping) following a prewarming phase to increase baseline core temperature by 1%.

These results show that prewarming followed by active warming is superior to passive warming in maintaining normothermia in anesthetized rats. Rats in the passive warming group showed a near linear decline in core temperature over the course of the 30 min anesthetic period, becoming hypothermic at around 30 min, and remaining so during the 30 min period after anesthesia. This decline in core temperature during general anesthesia highlights the limited effect of passive warming at prolonging normothermia after the prewarming period. While this may be acceptable for procedures lasting less than 30 min, even for such short procedures, body temperature should be closely monitored, and active heating provided during recovery, as temperatures may continue to fall after anesthesia.[31,42] In addition, the duration of normothermia will vary according to local factors such as environmental temperature, the invasiveness of procedure, and the animal's health status.

The benefits of maintaining normothermia are better established in humans than in animals. In humans, a reduction in core temperature of 1 °C is sufficient to cause numerous adverse outcomes, including myocardial ischemia, coagulopathy, significant thermal discomfort, delayed recovery, and increased surgical site infection, among others.[15,30,34] Hypothermia in animals has been linked to cardiovascular compromise, coagulopathy, increased data variability in biomedical research, and longer recoveries from anesthesia.[18,22,23,31,35,38]

Hypothermia is a well-recognized and extremely frequent anesthetic complication in animals, affecting as much as 84% to 97% of dogs and cats undergoing surgical procedures.[24,25,27] The rapid onset of hypothermia in anesthetized laboratory rodents suggests that a high incidence of hypothermia is likely if active warming is not provided.[2,6,31,36] Even when active warming is available, the temperature output of different devices can vary considerably, emphasizing the importance of temperature monitoring.[6,21,36,42] This variability was highlighted during our audit of the active warming blankets available in our institution. We found substantial differences in surface temperature between blankets, despite them all being programmed to deliver the same heat output.

Thermoregulation is normally tightly regulated in mammals, but this regulation is disrupted by general anesthesia with either inhaled or injected agents.[3,4,13,19,41] This disruption of thermoregulation allows a major redistribution of heat between the core

Table 1. Temperature recordings of the active warming systems (warming blankets)

Active warming device	Average temperature recorded for each section (°C)		
	Top	Middle	Bottom
1	22.7 ± 0.4	22.5 ± 0.4	22.1 ± 0.2
2	29.8 ± 0.2	29.2 ± 1.0	31.6 ± 1.4
3	36.1 ± 0.1	35.5 ± 0.2	36.9 ± 0.2
4	36 ± 0.2	35.5 ± 0.1	34.2 ± 0.2
5	36.2 ± 0.1	36.3 ± 0.1	36.4 ± 0.1
6	36.8 ± 0.6	35.6 ± 0.4	35.4 ± 0.2
7	37.6 ± 0.3	36.6 ± 0.7	36 ± 0.1
8	38.2 ± 0	37.1 ± 0.12	36.6 ± 0.1
9	34.8 ± 0.1	34.4 ± 0.1	34.2 ± 0.1
10	37.3 ± 0.2	36.3 ± 0.2	35.5 ± 0.3
11	33.7 ± 0.1	33.2 ± 0.1	32.9 ± 0.1
12	32.9 ± 0.1	32.4 ± 0.1	31.9 ± 0.1
13	34.3 ± 0.3	33.8 ± 0.1	33.4 ± 0.1
14	37.4 ± 0.3	36.3 ± 0.2	36 ± 0.2
15	37.2 ± 0.5	35.4 ± 0.1	35.0 ± 0.1
16	37.2 ± 0.2	36 ± 0.1	35.4 ± 0.2
17	37 ± 0.1	38.2 ± 0.3	38.4 ± 0.3
18	29.6 ± 0.4	37.3 ± 0.1	35.7 ± 0.3
19	37.1 ± 0.3	37.1 ± 0.3	36.6 ± 0.4
20	36.3 ± 0.2	37.2 ± 0.1	36.3 ± 0.2
21	39.1 ± 0.1	40.3 ± 0.4	38.7 ± 0.3

Recordings of the surface temperature of all active warming systems (warming blankets) that were available in our facilities. Data presented as mean ± SD.

and peripheral compartments, accounting for 80% of heat loss during the first hour of general anesthesia.[20] Recognition of this problem of heat redistribution after induction of general anesthesia has lead to the development of prewarming as a strategy to delay hypothermia.[9] Prewarming is based on the principle of decreasing the normal temperature gradient between the core and peripheral compartments, so that when thermoregulation is disrupted by the onset of anesthesia, minimal heat redistribution will occur. Reducing heat redistribution will thus slow heat loss to the environment, maintaining normothermia until reduced metabolic heat production causes body temperature to decrease.[37] This principle was illustrated in rats in this study by the observation that skin, core, and rectal temperatures all increased with prewarming.

Prewarming is known to be effective at maintaining normothermia in humans during general and spinal anesthesia.[5,7,9] However, the duration of effect in laboratory rats appears to be short.[28] In rodents, the limited literature available on temperature support during anesthesia focuses predominantly on the period after anesthesia has been induced. Compared with rats, differences in body mass and relative surface area may mean that mice become hypothermic more quickly but are also easier to warm and maintain in normothermia if active warming is provided.[6] In rats, active warming appears to be effective in limiting temperature loss during anesthesia, but does not prevent the initial drop in temperature associated with anesthetic induction or during the initial postanesthetic recovery period.[2,31] However, prewarming can be effective in preventing this initial fall in temperature.[31] Prewarming rats for 10 min (chamber temperature ranging from 35.7 to 37.5 °C) before transferring on to a heat pad (surface temperature, 36.9 °C) prevented hypothermia in rats during 40 min of general anesthesia and into the recovery period.[31]

The study reported here builds on this previous work by showing that passive warming, combined with prewarming, can delay the onset of hypothermia by approximately 30 min. The 1% prewarming target was less aggressive than that used previously,[28] and was based on evidence that rats prefer to face away from the incoming warmed air.[28] A drawback of passive warming is the possibility of hypothermia during recovery, as was observed here. Recovery from general anesthesia is not typically associated with a rapid return to normothermia[31] and active warming may be beneficial.[42]

This study has several limitations. First, although a negative control group (no prewarming, no passive warming) was not included for comparison, the development of hypothermia during general anesthesia (usually within 10 min of induction) is well established.[31,36] Second, recent work showed that the duration of normothermia after prewarming to a 1% target increase in core temperature may be limited to approximately 10 min.[28] This suggests that passive warming after prewarming does have a beneficial effect. The anesthetic and recovery periods in our study were limited to 30 min each. Thirty minutes was sufficient for the anesthetic period, as the data show core temperatures decreasing to a hypothermic level in the passive warming group, but a longer observation period after anesthesia would have been useful to establish the time required to return to baseline temperatures. Finally, all animals in the study were healthy, and no invasive procedures were performed. These considerations limit generalization of our findings to other situations; the larger surface area and direct exposure of the core to the environment during invasive procedures could result in a greater temperature reduction without active warming.

In conclusion, this study shows that a brief period of prewarming to increase of core body temperature to 1% above baseline, followed by passive warming with a fleece blanket is minimally effective in maintaining normothermia and does not prevent hypothermia during recovery. More effective temperature management can be achieved by using an active warming system after prewarming, potentially avoiding hypothermia in during anesthesia recovery period.

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