

Study of Two Devices Used To Maintain Normothermia in Rats and Mice During General Anesthesia

Douglas K Taylor

Rodents are very susceptible to hypothermia during anesthetic events because of their high body surface-to-mass ratio. This study examined the effectiveness of 2 heating devices, a heatpad and a circulating hot-water blanket, during 60 min of isoflurane general anesthesia in rats and mice ($n = 6$ per treatment). In addition, 1 control group of animals for each species was anesthetized with no heat source ($n = 6$). Both devices carried minimal risk of causing thermal burns or hyperthermia. Rats on the circulating water blanket showed a slight decrease (0.11 ± 0.19 °C) from the initial (time 0) body temperature (mean \pm standard error), whereas the heatpad was associated with a significant increase (0.96 ± 0.10 °C). Mice on the circulating water blanket showed a significant decrease (0.46 ± 0.05 °C) in body temperature. The trend in mice on the heatpad was similar to that in rats, with a significant increase (0.94 ± 0.13 °C) from the body temperature at time 0. Although statistically significant, these deviations from baseline body temperature were not considered physiologically relevant. In comparison, body temperatures decreased significantly in rats and mice (4.42 ± 0.60 and 9.90 ± 0.35 °C, respectively) with no heat source. Both heating devices were safe and effective, but the low cost, ease of maintenance, and portability of the heatpad may make it a more desirable choice in some facilities.

Rodent species used in biomedical research often undergo procedures that require the use of general anesthesia. General anesthesia subdues the mechanisms of thermoregulation,¹³ and thus maintenance of normal body temperature (normothermia) in patients is one of the principal challenges to the anesthetist. Small rodents, because of their relatively low body mass, have a high body surface area-to-mass ratio.^{4,12} This high ratio combined with suppressed thermoregulatory mechanisms allows for rapid escape of body heat in small rodents and consequently they are highly susceptible to hypothermia during anesthetic events.²

Small mammals can experience a decrease of 4 to 10 °C in core body temperature during only 15 to 20 min of general anesthesia, resulting in marked hypothermia.^{1,8,10} Hypothermia during anesthesia has several negative consequences for the patient. These include cardiac arrhythmias, increased susceptibility to infection, prolonged anesthetic recovery time, and decreased minimum alveolar concentration values for inhalant anesthetics, resulting in increased potential for anesthetic toxicity.^{1,2,15,21} These negative outcomes and the rapidity with which they can occur highlight the importance of providing rodents thermal support as soon as anesthetic induction has occurred.

Several heat-producing devices used to maintain rodent body temperature during general anesthesia have been described. These include heat lamps, electric heating pads, hot-air blankets, pocket warmers, and circulating hot-water blankets.^{3,6,11,23,24} The specifics regarding their use are principally anecdotal, and published data describing the safe use and effectiveness of such devices are sparse. Although any of the aforementioned devices can provide thermal support effectively, all carry a risk of inducing thermal skin injury and hyperthermia if used improperly. Close patient monitoring and careful attention to ambient temperatures generated by heating devices can miti-

gate these risks.

The present study examined the effectiveness of 2 commercially available heating devices in maintaining normothermia in rats and mice during 1 h of general anesthesia. One device, a circulating hot-water blanket, has traditionally been favored as a safe, reliable source of heat for rodents under general anesthesia.²³ The second device is a novel, microwaveable heatpad (SnuggleSafe Heatpad, West Sussex, UK) marketed in companion animal medicine and the pet trade as a device useful in warming pet bedding (Figure 1 A).

Materials and Methods

Heating device optimization. Prior to the initiation of animal studies, the heat generated by the heatpad at various microwave times was established so that no thermal injury to the animals would occur. Previous studies suggested that the temperature generated by any heating device with an animal present should not exceed a threshold temperature range of 40 °C (104 °F)¹ to 42 °C (107.6 °F).⁵ In light of these parameters, determination of a microwave time that generated a surface temperature equal to or slightly less than 40 °C with no animal present on the heatpad was the initial objective.

The heatpad was placed in the microwave oven (General Electric, Fairfield, CT) on 'high' power for 3 min, the maximal time recommended in the manufacturer's guidelines for the 1100-W microwave oven used in this study. Immediately after heating, the surface temperature of the heatpad inside the manufacturer's cover was measured every 15 min by use of an infrared thermometer (Raytek Raynger ST, Raytek Corporation, Santa Cruz, CA) until the heatpad cooled to room temperature (approximately 5 h later). Because 3 min of microwave time resulted in surface temperatures as high as 46.7 °C, surface temperatures generated with microwave times in 30-s decrements were subsequently measured; 1.5 min of microwave time produced surface temperatures of 37.2 to 38.9 °C. Because this

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Division of Animal Resources, Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA. Email: dtaylor@dar.emory.edu

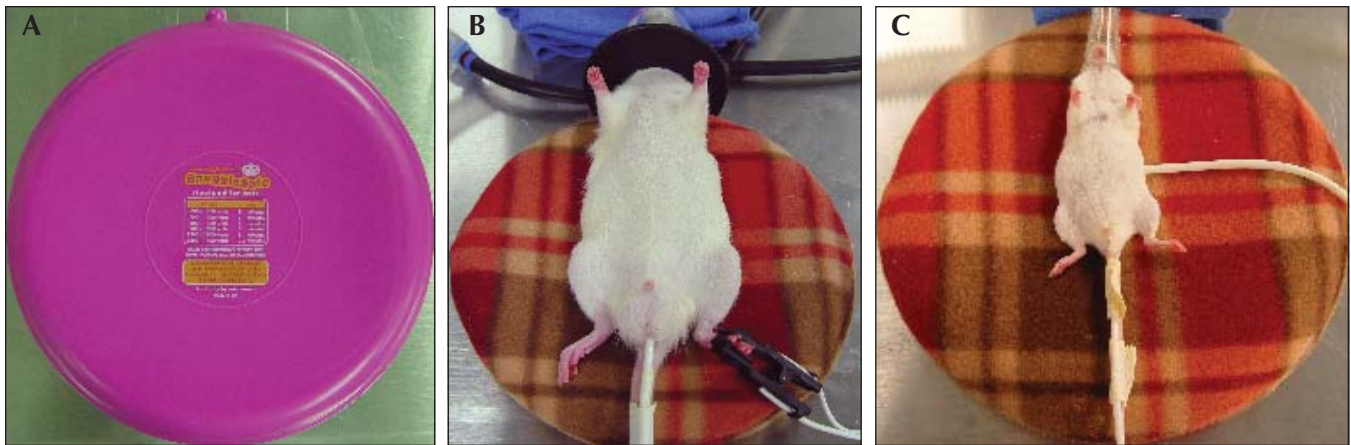


Figure 1. The heatpad used in this study, with (A) no cover and with manufacturer's cover when (B) rats and (C) mice were anesthetized.

range was close to but did not exceed the target temperature, a microwave time of 1.5 min was used for all experiments described that used the heatpad. The heatpad contained inside the manufacturer's cover was used in all experiments; it is reasonable to expect that the use of other types of cover materials could somewhat alter this heating profile.

Similar methodology was used to optimize the temperature settings for the circulating water blanket. For all experiments, a Gaymar T (Gaymar Industries, Orchard Park, NY) circulating water blanket was used. This particular model allows for selection of water temperature. A temperature setting of 102 °F (38.89 °C) was selected and produced water temperature of approximately 104.5 °F (40.28 °C) in the reservoir, according to a digital thermometer, and of approximately 100 °F (37.78 °C) at the surface of the water blanket, as measured using the infrared thermometer. As with the heatpad, these temperatures for the circulating water blanket were estimated to be sufficient to maintain body temperature without causing thermal injury to the patient.

Study design. Male and female Sprague–Dawley rats (age, 8 to 10 wk) and male CF1 mice (age, 6 to 8 wk) were used in this study. Body weight of each animal was recorded prior to experimentation, and the body surface area (BSA) was subsequently calculated using a published formula.⁴ All animals were housed in our facility, which is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International and were included in a protocol approved by the Emory University Institutional Animal Care and Use Committee. All rats and mice underwent routine quarterly (mice) or semiannual (rats) surveillance for a standard panel of infectious bacterial and viral diseases, ectoparasites, and endoparasites, and all results were negative throughout the history of the colonies from which study animals originated.

Animals were assigned randomly to 1 of 3 treatment groups ($n = 6$ per group): heatpad, circulating water blanket, and no heat source. All experiments were conducted in the morning at approximately the same time of day to avoid any influence of circadian rhythm on body temperature. Prior to induction of anesthesia, the temperature of the table top where all experiments were performed was measured by using the infrared thermometer and was consistently 70 to 72 °F (21.11 to 22.22 °C). Animals were anesthetized by placement into a clear, plastic induction chamber that was gradually instilled with isoflurane from a precision vaporizer. Anesthesia was maintained with a facemask at a depth such that the toe pinch reflex was absent.

Immediately after induction, animals were placed on the heatpad (Figure 1 B, C), circulating water blanket, or surgical

table top with no heat source, and initial measurements (T0) of all parameters were taken. Subsequent measurements were made in 5-min increments for 60 min (T5 through T60). For both the heatpad and water blanket, the surface temperature of the heating device with the animal present was measured by placing a thermistor probe (YSI Incorporated, Dayton, OH) between the animal and heating device at approximately mid-abdomen. To measure body temperature, a thermistor probe was positioned rectally. In addition, heart rate and blood oxygen saturation (SpO_2) were monitored, although reliable SpO_2 values could not be obtained in the mouse due to the small size of these animals. SpO_2 , heart rate, and body and heating device temperature values were displayed (Surgivet V9204 monitoring system, Smith's Medical PM, Waukesha WI). Respiratory rate was measured by observation and auscultation in both rats and mice. Animals were euthanized after 60 min by CO_2 overdose while anesthetized.

Statistical analysis. Repeated-measures analysis of variance with Tukey post-hoc tests for pairwise comparisons was performed to compare treatment groups at each time point and to compare T0 with other time points within each treatment group (GraphPad Software, San Diego, CA). A P value of less than 0.05 was considered statistically significant. Pearson correlation analysis showed no significant effects of body weight, body surface area, or gender.

Results

Rats. The body temperature (mean \pm standard error) at T0 for all rats across treatments was 36.65 ± 0.39 °C, which is very nearly within their normal range of 37 to 38 °C (98.6 to 100.4 °F).¹ Body temperature at T5 through T60 for animals placed on either the circulating water blanket or heatpad was maintained, and a striking drop in body temperature occurred throughout the duration of each experiment when no heat source was present.

The circulating water blanket showed remarkably little deviation from the T0 temperature of 36.78 ± 0.45 °C throughout the 60-min time period; the largest deviation in body temperature was a slight and nonsignificant decrease of 0.11 ± 0.19 °C to 36.67 ± 0.26 °C at T20. In addition, differences between T0 and all other time points were not statistically significant. With the use of the heatpad, body temperature never decreased from the T0 value of 37.03 ± 0.53 °C, and the largest deviation was a significant ($P < 0.001$) increase of 0.96 ± 0.10 °C to 37.99 ± 0.63 °C, which occurred at T50 (Figure 2 A). In addition, differences between T0 and each of the time points T20 through T60 were statistically significant ($P < 0.001$).

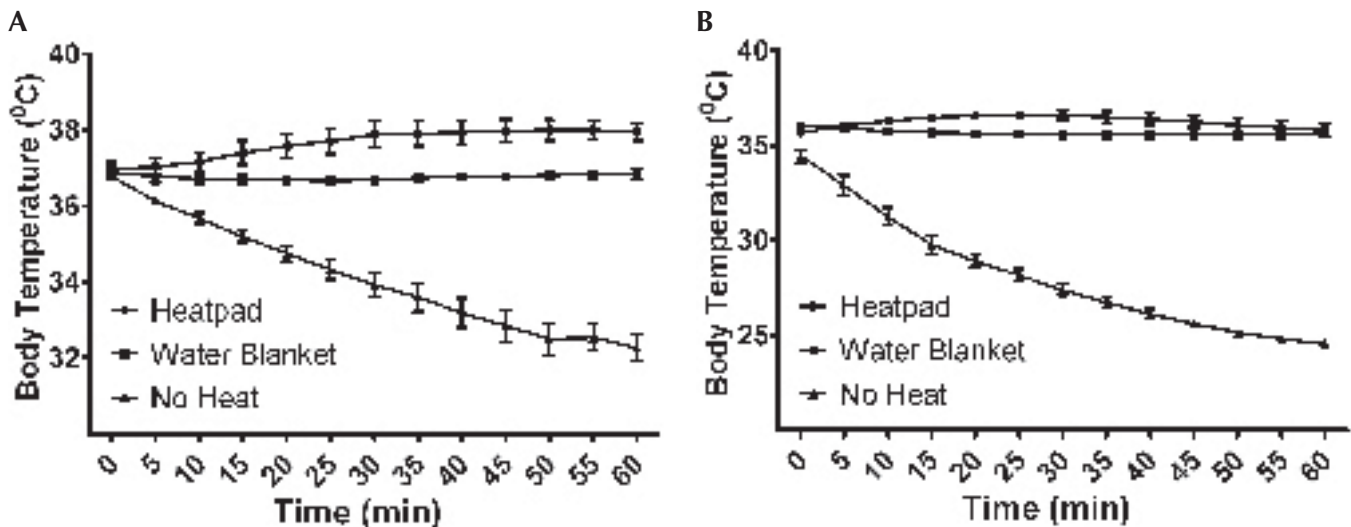


Figure 2. Both the heatpad and circulating water blanket were effective in maintaining normothermia in (A) rats and (B) mice during 1 h of general anesthesia. Body temperatures of animals on the heatpad (circles) never decreased after time point T0, whereas a slight and insignificant decrease from T0 occurred with use of the circulating water blanket (squares) for both rats and mice. In contrast, significant hypothermia occurred when no thermal support (triangles) was provided.

In contrast to the stability in body temperature observed with thermal support from either the water blanket or the heatpad, body temperature dropped progressively over time when no heat source was used. Body temperature dropped steadily from 36.75 ± 0.20 °C at T0 to 32.33 ± 0.80 °C at T60, a significant ($P < 0.001$) decrease of 4.42 ± 0.60 °C. In fact, the differences between T0 body temperature and all points from T10 through T60 were statistically significant ($P < 0.01$). All other physiologic parameters measured remained normal throughout all experiments, with the exception of mild bradycardia that was typically noted from T45-T60 in the no-heat group (data not shown).

Statistically significant ($P < 0.05$) differences in body temperature occurred between rats in the water blanket and heatpad treatment groups at time points T20 through T60 (Figure 2 A). Even more remarkable were the differences in body temperature between animals that received either form of thermal support and those that had no heat source; these differences were statistically significant ($P < 0.001$) at all time points beyond T5. Taken as a whole, these findings suggest that both methods of thermal support in rats were effective in maintaining normothermia during 1 h of general anesthesia, and both were superior to a complete absence of heat source.

From T0 through T60, the temperature as measured at the surface of the circulating water blanket with rats present was quite stable, ranging from 37.28 to 38.17 °C, whereas heatpad temperatures were less stable, ranging from 38.94 to 42.72 °C. Minimal temperature fluctuation occurred with the water blanket, whereas the heatpad exhibited a characteristic heating and cooling profile, with lower temperatures during early and late time points and higher temperatures during middle time points (data not shown).

Mice. The average body temperature at T0 for all mice across treatments was 35.39 °C, which was lower than the reported normal range of 37.11 to 37.50 °C.¹ Similar to the outcomes with rats, body temperature at T0 through T60 for mice placed on either the circulating water blanket or the heatpad was maintained reliably, but body temperature dropped remarkably throughout the duration of each experiment when no heat source was present.

With the circulating water blanket, there was a slight but steady decline from the T0 temperature of 36.03 ± 0.50 °C to the lowest temperature of 35.57 ± 0.45 °C at T45 and T50, a

decrease of 0.46 ± 0.05 °C that was statistically significant ($P < 0.001$) (Figure 2 B). In addition, differences between T0 and all subsequent time points were statistically significant. The body temperature trend in mice on the heatpad was similar to that seen in rats. Specifically, body temperature never decreased from the initial body temperature of 35.69 ± 0.49 °C, and the largest deviation was a statistically significant ($P < 0.01$) increase of 0.94 ± 0.13 °C to 36.63 ± 0.62 °C, which occurred at T30 (Figure 2 B). In addition, differences between T0 and each of the time points T15 through T35 were statistically significant ($P < 0.001$).

As with rats, the body temperatures of mice dropped rapidly when no heat source was used, and the magnitude of the decrease was greater in mice. Body temperature dropped steadily from an average of 34.44 ± 0.85 °C at T0 to 24.54 ± 0.50 °C at T60, a decrease of 9.90 ± 0.35 °C, which was statistically significant ($P < 0.001$). Furthermore, the differences between body temperature at T0 and those at all points from T5 through T60 were statistically significant ($P < 0.01$).

There were statistically significant differences ($P < 0.05$) in body temperature at time points T25 and T30 between the water blanket and heatpad treatment groups (Figure 2 B). Even more remarkable were the differences in body temperature between animals that received thermal support by either of the devices and those that had no heat source; these differences were statistically significant ($P < 0.05$ to 0.001) at all time points (Figure 2 B). Taken together, these data suggest that both methods of thermal support in mice are equivalent in their ability to maintain normothermia in mice during 1 h of general anesthesia, and both heat sources are superior to a complete absence of heat source.

The temperatures measured at the surfaces of both heat sources with mice present were comparable to those in rats, with minor exceptions. The temperature measured at the surface of the circulating water blanket with mice present ranged from 35.83 to 38.06 °C, whereas the temperature at the surface of the heatpad ranged from 32.67 to 40.17 °C. The temperature ranges for heat sources were greater with mice than rats, but the highest temperature generated by the heatpad was 2.55 °C less with mice. In close agreement with observations in rats, less temperature fluctuation occurred with the water blanket than the heatpad, which again exhibited the characteristic heating and cooling profile in mice that was seen with rats.

Discussion

There were 2 principle objectives for this study. The first was to determine conditions under which the heatpad could be used safely to provide thermal support to rats and mice under general anesthesia. The second objective was to determine whether the heatpad, a novel device, and the circulating water blanket, the heating device considered by many to be the safest and most effective way to provide heat to rodents during general anesthesia, were comparably effective in maintaining normothermia. This study showed that both heating devices can provide safe and effective thermal support for rats and mice with minimal fluctuation in body temperature through 60 min of general anesthesia when used properly.

To determine whether there was significant risk of thermal burns when using the heatpad or water blanket, the surface temperature of each device was measured when animals were present. Thermal skin injury occurs as a function of temperature and contact time. For example, irreversible skin damage will occur in humans after approximately 6 h at a threshold temperature of 44 °C (111.2 °F).¹⁷ If the temperature is below threshold, or contact time is reduced, no skin injury will occur. For the group of rats placed on the heatpad, there was a 0.72 °C excursion above the desired 'safe' maximum of 42.0 °C⁵ that occurred for 20 min in only 1 animal; 42.0 °C⁵ was not exceeded in any other animal across all experiments. The published literature provided no data regarding the combined effect of contact time and temperature causing thermal injury in animals, although the principles for humans presumably apply to animal species. Without such data and because thermal injury was not an endpoint measured in this study, it is difficult to determine if there was any significant risk of injury to the 1 animal exposed to a temperature of 42.72 °C for 20 min. It seems reasonable to conclude that the risk of thermal injury to this animal was minimal given the small magnitude of the temperature elevation over a short period of time. Solutions to this potential problem include reducing heatpad microwave time and the use of additional layers of materials between the heatpad and animal.

In addition to thermal burns, hyperthermia is another possible negative outcome associated with poorly executed thermal support during general anesthesia. Because the core body temperature of any anesthetized patient is very susceptible to ambient temperature influences,² exposure to excessive heat can result in hyperthermia. However, with the exception of malignant hyperthermia in humans and pigs^{7,16} and postanesthetic hyperthermia in cats,⁹ neither of which occur as a function of the heat applied during anesthesia, the published literature doesn't address the issue of hyperthermia during general anesthesia. Although this dearth of information might imply that external heat source-associated hyperthermia is a problem encountered rarely, this outcome is nonetheless a real concern with rodent anesthesia, and deaths can result.¹⁹

In this study, slight but statistically significant increases in body temperature occurred during use of the heatpad; body temperature rose 0.96 ± 0.10 °C in rats and 0.94 ± 0.13 °C in mice. These increases are minimal compared with those seen in cases of malignant hyperthermia in humans and pigs, where body temperatures of 45.0 to 46.11 °C (113 to 115 °F) have occurred,^{7,20} or postanesthetic hyperthermia in cats where body temperature can reach 42.5 °C (108.5 °F),⁹ or even those associated with heat stroke in humans, when body temperature reaches 40.0 to 41.0 °C (104.0 to 105.8 °F).^{18,25} The increases seen during these life-threatening cases of hyperthermia represent a 7% to 9% increase in body temperature. Increases of the same magnitude in rats and mice would result in body temperature

values as high as 41.42 °C and 40.88 °C, respectively. It therefore seems reasonable to conclude that the slight increases that occurred during this study, while statistically significant, were not physiologically relevant or life-threatening.

Having established that the heatpad and circulating water blanket could indeed be used safely, the next question to address was whether they are equally effective in maintaining normothermia. Normothermia is defined as the condition of normal body temperature. Because 'normal' body temperature ranges are, in essence, statistical averages, an individual's temperature does not always fall directly within published normal ranges as was seen in this study at T0, the time when body temperature should have been essentially 'normal'. One of the true objectives of this study was to safely prevent hypothermia, rather than to maintain perfect normothermia. For this reason, in order to determine if the heating devices were effective in maintaining body temperature, values at T0, not published normal values, were used as the reference point against which all subsequent measures were compared.

Body temperature decreased slightly in both rats and mice with the use of the water blanket but not at all using the heatpad. In humans, decreases in body temperature of 3 °C (5.4 °F), a 5.5% reduction, are common during general anesthesia and surgical procedures.¹³ Mild hypothermia in humans occurs at a body temperature of 32 to 36 °C,^{14,21} and life-threatening hypothermia occurs below 32 °C,²¹ which is a decrease in temperature of approximately 14%. In light of these data, the slight decreases in body temperature of 0.11 ± 0.19 °C and 0.46 ± 0.05 °C (reductions from T0 of 0.4% and 1.2%, respectively) that occurred in rats and mice respectively using the hot-water blanket, although statistically significant for mice, were likely irrelevant physiologically.

In contrast, when no heat source was present, the resultant reductions in body temperatures were almost certainly physiologically significant, because animals consistently exhibited bradycardia by the end of each experiment. Although the maximal reduction seen at T60 in rats was 8% and could be classified as mild hypothermia, mice demonstrated a 19% reduction in body temperature for mice at T60, which can be considered life-threatening. In fact, body temperature in mice at T35 had already decreased by 14% of that at T0, to 26.72 ± 0.66 °C. These reductions in the absence of thermal support were comparable to the 4 to 10 °C drop in body temperature during 15 to 20 min of general anesthesia reported elsewhere.^{1,8,10} Although time of recovery from anesthesia was not measured in this study, prolongation would be reasonably expected in these hypothermic animals. Taken as a whole, these data show that each heating device effectively prevented hypothermia and that significant hypothermia will occur in rats and mice not provided thermal support over even short periods of general anesthesia. It seems clear, then, that the provision of thermal support will reduce the risk of negative outcomes associated with general anesthesia.

Beyond their comparability in safety and effectiveness, there are some important practical distinctions to be made between the heatpad studied and circulating water blankets. The heatpad was purchased for \$25, whereas the circulating water blanket pump used in this study cost \$359, with blankets as an additional cost. This difference makes the heatpad very cost-effective to use. The need for a microwave oven to prepare the heatpad adds some expense, but most laboratories and animal facilities already have this appliance at their disposal. Furthermore, the heatpad is small, portable, and easy to clean, compared with the water blanket. One disadvantage of the heatpad is its relatively small size, which makes it less than ideal for use with very large

rats or larger rodent species such as guinea pigs. A second possible disadvantage is that the microwave time that produces safe levels of heat must be determined before the heatpad can be used with animals.

This study showed that both the heatpad and circulating hot-water blanket were safe and effective in providing necessary thermal support. For the heatpad, 1.5 min of time in an 1100-W microwave produced positive results. Both the microwave wattage and heating time will affect the heating profile of this device, and predetermining the amount of microwave time necessary to produce a safe level of heat (as was done in this study) is very important for animal safety. For the water blanket, a temperature setting of 102 °F (38.89 °C) produced similarly favorable results. Users need to be aware that the amount of material between any heating device and animal, presence of surgical drapes, and exposure of body cavities during surgery can dramatically affect heat loss from the patient. Monitoring of patient body temperature and the development of standard procedures are always recommended to ensure the safe use of the devices described in this report or any other heating device.

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