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Sede Amministrativa Università degli Studi di Padova

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Indirizzo in Scienze Cliniche Veterinarie

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TESI DI DOTTORATO

**Effect of pre-warming on the body temperature of small animals
undergoing general anaesthesia**

Direttore della Scuola: Ch.mo Prof. Gianfranco Gabai

Coordinatore d'indirizzo: Ch.mo Prof. Maurizio Isola

Supervisore: Ch.mo Prof. Roberto Busetto

Co-supervisor: Dottoressa Colette Jolliffe

Dottoressa Elizabeth A Leece

firme

Dottorando: Clara Francesca Rigotti **966268-DR**

firma

*The recognition of the existence of a
problem is the first step in it's solution.*

Martin H Fischer

CONTENTS

1. ABSTRACT	7
1. RIASSUNTO	9
2. INTRODUCTION	11
2.1 Normal thermoregulation	11
2.2 Hyperthermia	19
2.3 Temperature distribution	21
2.4 Thermoregulation during general anaesthesia	22
2.5 Considerations in pediatric patients	28
2.6 Considerations in elderly patients	29
2.7 Drug influences on thermoregulation	30
2.8 Temperature monitoring	34
2.9 Complications of perioperative hypothermia	36
2.10 Prevention and treatment of hypothermia	42
2.11 Postoperative considerations	48
3. AIM OF THE STUDY	50
4. MATERIALS AND METHODS	51
4.1 Animals and inclusion criteria	51
4.2 Study groups	52
4.3 Protocol	53
4.4 Statistical analysis	56
5. RESULTS	58
6. DISCUSSION AND CONCLUSION	67
6.1 Study design	67
6.2 Results	70

1. ABSTRACT

Pre-warming may reduce hypothermia during anaesthesia in humans (Andrzejowski et al. 2008). A prospective, randomised, blinded, clinical trial investigated the effect of pre-warming on body temperature in small animals undergoing anaesthesia.

Dogs and cats ASA I-II, weighing <10kg undergoing minor procedures without extensive clipping were enrolled. Baseline rectal temperature was recorded. Following sedation (buprenorphine and acepromazine IM), dogs and cats were block randomised according to weight into two groups: pre-warming group (30 minutes in incubator, temperature 33°C) and control group (no pre-warming). Body condition score (BCS) and sedation were scored. Anaesthesia was induced with alfaxalone IV and maintained with isoflurane in oxygen. Rectal, oesophageal and ambient temperature were measured every 5 minutes from induction by an observer unaware of treatment. Animals were withdrawn from the study if oesophageal temperature was <36°C. Data for cats and dogs were analysed separately. After normality testing, groups were compared using t-tests or Mann Whitney ($P<0.05$). From induction to 60 minutes, temperatures were compared using ANOVA with post-hoc Bonferroni correction. Fisher's exact test was used to assess the proportion of animals withdrawn because of hypothermia.

Thirteen cats and ten dogs were pre-warmed, twelve cats and nine dogs were controls. There were no differences between groups for age, weight, BCS, sedation score, time from sedation to induction or anaesthesia duration. Time between removal from the incubator and induction was 19.6 ± 7.2 minutes in cats and 23 ± 12.5 minutes in dogs. Oesophageal and rectal temperatures were similar between groups during the first hour of anaesthesia. Ambient temperature was lower in controls compared to pre-warmed dogs throughout the study, and higher in controls compared to pre-warmed cats from 5 minutes ($P < 0.05$). The incidence of hypothermia was similar in both groups.

Pre-warming in an incubator for 30 minutes failed to improve body temperature during anaesthesia.

1. RIASSUNTO

Nell'uomo è stato dimostrato che il riscaldamento pre-operatorio riduce l'incidenza di ipotermia in soggetti sottoposti ad anestesia generale (Andrzejowski et al. 2008). E' stato condotto uno studio clinico cieco, prospettico, randomizzato, per valutare l'effetto del riscaldamento pre-operatorio sulla temperatura dei piccoli animali sottoposti ad anestesia.

Nello studio sono stati inclusi cani e gatti clinicamente sani con peso inferiore a 10 kg, anestetizzati per procedure diagnostiche o chirurgie minori. E' stata misurata la temperatura rettale di base. Dopo sedazione con acepromazina e buprenorfina intramuscolare, cani e gatti sono stati rispettivamente randomizzati in due gruppi: gruppo riscaldato pre-operatoriamente (30 minuti in incubatrice con temperatura di 33°C) e gruppo di controllo (nessun riscaldamento pre-operatorio). Sono stati valutati il Body condition score (BCS) ed il livello di sedazione. L'anestesia è stata indotta con alfaxalone somministrato per via endovenosa e mantenuta con isoflurano vaporizzato in ossigeno.

Le temperature rettale, esofagea ed ambientale sono state misurate ogni 5 minuti a partire dall'induzione, da un osservatore non a conoscenza del trattamento. Se la temperatura dell'animale scendeva sotto i 36°C, lo studio veniva interrotto. I dati di cani e gatti sono stati analizzati separatamente. Dopo aver testato la normalità dei dati, i gruppi sono stati valutati usando t-test o Mann Whitney ($P < 0.05$). Per la prima ora di anestesia, le temperature sono state confrontate usando ANOVA con correzione post hoc Bonferroni. Fisher exact test è stato utilizzato per valutare la proporzione di animali rimossi dallo studio a causa di ipotermia.

Tredici gatti e dieci cani hanno ricevuto riscaldamento pre-operatorio, dodici gatti e nove cani erano controlli. Non c'è stata differenza tra i gruppi per quanto riguarda età, peso, BCS, livello di sedazione, tempo tra sedazione ed induzione o durata di anestesia. Il tempo tra rimozione dall'incubatore ed

induzione dell'anestesia è stato 19.6 ± 7.2 minuti per i gatti e 23 ± 12.5 minuti per i cani. La temperatura esofagea e rettale sono state simili durante la prima ora di anestesia. La temperatura ambientale è risultata inferiore nei cani del gruppo di controllo rispetto ai cani riscaldati pre-operatoriamente e superiore nei gatti di controllo rispetto ai gatti riscaldati pre-operatoriamente a partire da 5 minuti ($P < 0.05$). L'incidenza di ipotermia è stata simile in entrambi i gruppi.

Il riscaldamento pre-operatorio in incubatrice per 30 minuti non ha migliorato la temperatura durante l'anestesia.

2. INTRODUCTION

Accidental hypothermia during anaesthesia is an unintentional fall in the body temperature below normal and was first recognised by Von Kappeler in 1880 (Newman 1971).

Hypothermia, in humans, has been defined as a decrease in body temperature below 37°C (Matsuzaki 2003). The normal canine and feline temperature range varies between 37.8°C and 39.2°C. In veterinary patients, mild hypothermia has been defined as temperature between 37°C and 32°C, moderate hypothermia was considered a temperature between 32°C and 28°C, while severe hypothermia was a temperature below 28°C (Oncken 2001).

Perioperative hypothermia is a common complication in human surgical patients, with an incidence of 60 to 80% (Matsuzaki 2003). Although the incidence in veterinary patients has not been documented, it is probably similar to that of humans (Armstrong 2005).

2.1 NORMAL THERMOREGULATION

2.1.1 Temperature control

Body tissues produce heat proportionally to their metabolic rates. The First Law of Thermodynamics states that the energy generated by a chemical reaction is determined only by the substrates and products of the reaction. Almost all this energy is eventually converted into heat. The major substrates for human metabolism are glucose, protein and fat and the main products of aerobic metabolism are carbon dioxide and water. The combustion of glucose and protein produces 4.1 kcal/kg, whereas fat releases 9.3 kcal/kg.

The brain and major organs in the trunk are the most metabolically active tissues and they generate more heat than muscle at rest.

Mammalian body temperature is maintained close to a strict range at which cellular function is optimal. Temperature regulation is even more precise than blood pressure or heart rate range. The control involves positive and negative feedback systems that are so widely distributed that nearly every part of the autonomic nervous system is involved to some extent.

Already in 1912 it was known that the hypothalamus was the dominant thermoregulatory centre in mammals, because temperature control was markedly compromised by lesions in this area. It was only half a century afterward that the importance of the thermal input from the skin was appreciated. Now there is evidence that thermal impulses from a variety of tissues contribute to thermal control with the hypothalamus, and that there is an elaborate pre-processing of thermal information from peripheral to central tissues (Satinoff 1978).

Several complex mechanisms are involved in temperature control, of which the hypothalamus is the regulatory centre. Hypothalamus responds to local changes in temperature but also to neural input from thermal receptors in different parts of the body.

To maintain a constant temperature heat production and heat loss need to be matched. Temperature is regulated largely by control of heat lost from the body surface via conduction, convection, evaporation and radiation. Heat is lost also from the respiratory tract and in urine and faeces.

If the body becomes too cold, heat is retained through peripheral vasoconstriction to avoid warm blood to reach the cooler periphery; muscle activity like shivering, voluntary movement and piloerection which insulate the skin by trapping a layer of stationary air. Chemical thermogenesis (adrenergic) may also play a part. Behavioural responses to cold are extremely important, for example curling up, moving into a warm shelter and lying close to other animals.

Heat is lost by opposite processes, such as vasodilation of superficial blood vessels, panting and sweating to increase heat evaporation.

The processing of the thermoregulatory information is divided into three phases:

1. afferent input
2. central regulation
3. efferent responses

1. Afferent input

There are specific cells that respond to temperature changes by activation or inhibition; these cells are temperature sensors and they can be either warm or cold sensing cells. Cold receptors, for instance, will increase their activity when temperature decreases and the opposite is true for heat receptors.

Because it is easy to access, cutaneous thermoreception has been widely studied.

In humans, skin temperature perception and its ability to influence the hypothalamic control is not uniform across the body surface. The face, perhaps, is five times as sensitive as other areas. Furthermore, the skin is much more sensitive to sudden temperature changes compared to those occurring slowly.

The fundamental thermal receptors, both on the skin and on the dorsal root ganglia, appear to be the Transient Receptor Potential (TRP) vanilloid (V) and menthol (M) receptors. This receptor family is known for having an unusually high temperature sensitivity; TRPV 1-4 receptors are heat activated, whereas TRPM 8 and TRPA 1 respond to cold (Brauchi 2006, Moqrich 2005).

Cold signals from the skin are transduced by A δ afferent nerve fibres and warm signals travel via un-myelinated C fibres (Paulos1981). Most ascending thermal information traverses the spino-thalamic tracts in the anterior spinal cord, but there is not a single spinal tract which is critical to convey the thermal information.

Together with the skin, the hypothalamus, other brain areas, the spinal cord, deep abdominal and thoracic organs contribute roughly a fifth each of the total thermal input to the central regulatory system (Jessen 1984, Simon 1974).

Although the hypothalamus is the most important regulatory centre, its temperature per se is not particularly important.

2. Central control - Thermoregulation models

Set point system

This is the simplest thermoregulatory model in which all the signals are turned on or off in response to hypothalamic temperature. This is an inadequate representation of the thermoregulatory system for several reasons. First of all the thermal responses are mediated by inputs coming from nearly every portion of the body and they are not activated simultaneously or at similar temperatures. The model does not incorporate a “null zone” in which no thermoregulatory responses are activated and it cannot explain the phenomenon of thermal adaptation (Sessler 2008).

The general thermoregulatory model

This is a more complicated model but considerably more useful. As a model, it should be considered a framework to analyse thermoregulatory responses, not a mechanism by which the body produces these responses. In this model, thermal input from the different part of the body is integrated in multiple centres, most importantly in the hypothalamus. The individual responses are coordinated on the basis of weighted averages of the diverse inputs.

Temperature is regulated by central structures, at various levels in the neuraxis, that integrates thermal inputs from skin, neuraxis and deep tissues with different thresholds for each thermoregulatory response. The dominant controller in mammals is the hypothalamus, with autonomic control centred in the anterior hypothalamus and behavioural control in the posterior hypothalamus (Satinoff 1978).

It is likely that some responses can be activated by the spinal cord alone, for example animals with high spinal cord transections regulate temperature worse than normal, but are not poikilothermic (Simon 1974).

About 80% of the control of autonomic responses is determined by thermal input from core structures (Cheng 1995, Wyss 1975) and remain similar during general anaesthesia. On the other hand, half of the input controlling behavioural responses is derived from the skin surface.

In humans normal core temperature ranges from 36.5°C to 37.5°C (interthreshold range); values < 36°C or >38°C indicate loss of control or an extreme thermal environment which overcomes thermoregulatory defences. The temperature range varies between species with the extreme of camels, which allow body temperature to change up to 10°C during a 24 hour period. This model does not adequately account for the rate at which central and peripheral temperature changes. Usually thermoregulatory responses are not determined only by the instantaneous thermal input, but they also reflect the recent history of thermal perturbation. The extent to which factors depending on time and temperature contribute to human thermoregulation remains unclear.

Thresholds

In humans the threshold varies during the day with a circadian rhythm by 0.5-1°C (Tayefeh 1998). Several factors can alter the temperature threshold, like exercise, nutrition, infection, endocrine disorders, drugs and cold/warm adaptation. Each of these effects is small compared with the profound impairment produced by general anaesthesia.

The interthreshold range is defined as the range in which core temperature does not trigger an autonomic response. This range is bounded by the sweating threshold at its upper end and by the vasoconstriction threshold at the lower end.

Central thermoregulatory control may be influenced by age. It seems to be intact even in slightly premature infants (Mestyan 1964), but it is immature in smaller infants such those weighing less than a kilogram. Also the shivering threshold appears to be well maintained in some elderly subjects whereas others have a poor regulation; overall regulation is generally normal in people aged less than 80 years.

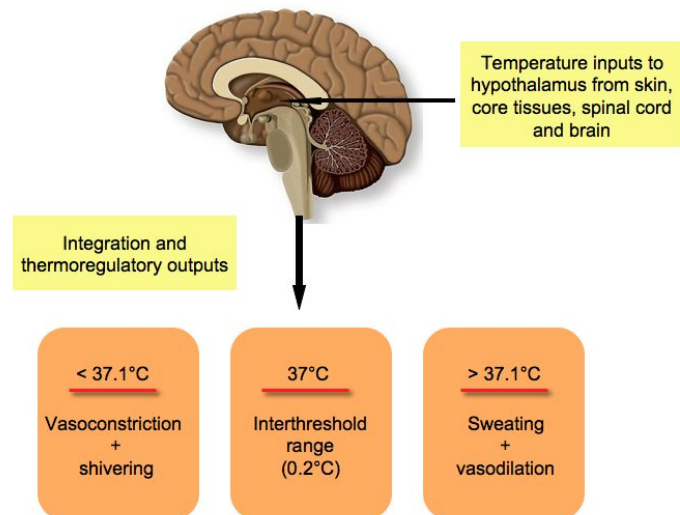


Figure 1. Hypothalamic thermoregulation. Temperature inputs to the hypothalamus are integrated and compared with threshold temperatures that trigger appropriate thermoregulatory responses. Normally, the responses are initiated when the temperature is only 0.1°C above or below the normal threshold. Therefore the difference in temperature that initiate sweating and shivering is of only 0.2°C (Diaz 2010).

3. Efferent responses

Behavioural regulation

When autonomic thermoregulatory responses are insufficient for maintaining central temperature, behavioural responses become critical for survival.

This is the most powerful thermoregulatory response and it is most dramatic in reptiles and amphibians. These cold blooded animals regulate their temperature positioning themselves to maintain a central temperature within a few degrees of normal range (Smith 1998). Similarly fish provided with a thermal gradient will position themselves to maintain a constant body temperature (Rausch 2000).

For a behavioural response, a conscious perception of body temperature is required. In mammals this mechanism is half mediated by skin temperature (Frank 1999), whereas mean-skin temperature contributes only about 10-20% to the control of autonomic thermoregulatory defences (Cheng 1995).

Vasomotion

Most of the metabolic heat is lost through the skin surface and cutaneous vasoconstriction helps to reduce this loss. The total digital skin blood flow is divided into two components: nutritional (mostly capillary), and thermoregulatory (mostly arterio-venous shunt) (Hales 1985). The flow of the arterio-venous shunt is typically “on” or “off”, and they receive about 10% of the cardiac output. Consequently, shunt vasoconstriction increases mean arterial pressure by roughly 15 mmHg (Greif 2003). These specialized thermoregulatory vessels are controlled by α adrenergic fibres and respond with vasoconstriction to the release of noradrenaline. Most blood vessels constrict in response to regional hypothermia, but arterio-venous shunt are particularly resistant to local temperature changes and appear to respond almost exclusively to central thermal status. In a thermoneutral environment the shunts are almost fully dilated. Therefore, they function as effector organs for dissipation or conservation of heat to help maintain normothermia. The distal extremities of humans and many animals contain a richer supply of arterio-venous shunts compared to head and trunk (Spence 1972, Sessler 1990). The large network of shunts located in these thermosensitive areas contain as much as 80% of the blood flow to that region, depending on the level of vasodilation. With the development of hypothermia, shunt vasoconstriction is sufficient to reduce cutaneous heat loss by 17% in the regions of the head and trunk, and 25% to 50% in the extremities (Sessler 1990).

Non-shivering thermogenesis

It is defined as an increase in metabolic heat production not associated with muscular activity. This process is typical of the brown adipose tissue, located in the intrascapular and perirenal regions. Brown fat has a dark hue due to its high concentration of mitochondria; when stimulated, it has the highest metabolic rate of any organ (Nedergaard 1992).

Non-shivering thermogenesis is the primary defence against cold in infants (Dawkins 1965) and small mammalian species (mice, rats) in which can double or triple the metabolic heat production without producing any

mechanical work. In adults or in animals of large size (>50 kg) the non-shivering thermogenesis is poorly developed and not efficient (Jessen 1980).

Shivering

Sustained muscle contractions occurring during shivering increase metabolic heat production by 50 to 100 % in adults. Shivering does not occur in neonates or infants and it is probably not fully effective until children are several years old. This appears to be the last resort in response to extreme cold, as the shivering threshold is a full degree less compared to the vasoconstriction threshold (Lopez 1994).

Sweating

Sweating is mediated by post-ganglionic cholinergic nerves (Hemingway 1968). In humans, sweating is the only mechanism by which the body can dissipate heat in an ambient exceeding core temperature. The sweating threshold is similar to the one for active vasodilation, which usually is delayed until sweating intensity is at its maximum.

Domestic animal species, which cannot dissipate heat with sweating, cool down with panting. Panting is a controlled increase in respiratory frequency associated with a decrease in tidal volume with the aim to increase the ventilation of the upper respiratory tract, to preserve alveolar ventilation and thereby to increase evaporative heat loss (Robertshaw 2006). Schmidt-Nielsen et al (1970) demonstrated that during thermal panting most of the air enters the nose and leaves the mouth. The nasal cavity seems to be the primary site of evaporation, as most of the heat exchange takes place at the nasal epithelial lining. There are two lateral nasal glands that provide a large part of water for evaporative cooling during panting; their function is the same of that of sweat glands in man (Blatt 1972).

2.2 HYPERTHERMIA

Hyperthermia indicates a core body temperature that exceed the normal range for that species. It is considered different from fever, which is an increased in body temperature regulated at the level of the central thermoregulatory system. In the hyperthermic states other then fever, hyperthermia is not the result of the body attempting to raise its temperature, but is due to the physiologic, pathologic or pharmacologic intervention where heat gain exceeds heat loss (Miller 2005).

Passive hyperthermia

Passive intraoperative hyperthermia results from excessive patient heating and it is more common in small breed patients or in large and long coated breeds. Passive hyperthermia in large breeds is facilitated by the use of a circle breathing system with low fresh gas flow and also by positioning a heat and moisture exchanger between patient and circle. It is usually exacerbated by a warm environment, and can be easily treated by discontinuing the active warming and if necessary administering cold fluids, high fresh gas flows or applying cold packs on the patient's body.

Heat stroke

Heat stroke is a common form of inadequate heat dissipation. Exposure to high ambient temperatures may increase body heat content at a faster rate than the body can dissipate. This is typical in large breeds, especially brachycephalic dogs, left in non ventilated hot environments (inside a car). The animal must be treated with full body cooling with intravenous fluids, enema and body rinses with cool water. The temperature of the water should not be too cold, to avoid causing vasoconstriction limiting heat dissipation (Miller 2005).

Excessive heat production

Hyperpyrexia syndrome is associated with exercise in a hot and humid environment, typical of hunting dogs or dogs that jog with their owners. In humid environments there is a tendency to reach a zero thermal gradient for

dry heat loss leading to a net heat gain. In addition, during severe exercise, blood flow to skeletal muscle is high, while peripheral heat loss is compromised by inadequate vasodilation at the level of the skin. Hyperthermia can develop also during severe exercise in normal ambient temperature due to increased muscular activity (Miller 2005).

Malignant hyperthermia

Malignant hyperthermia leads to a myopathy and subsequent metabolic heat production, secondary to disturbed calcium metabolism that can be initiated by several causes, including pharmacologic agents such as inhalational anaesthetics (especially halothane). Extreme muscle rigidity may or may not be present (Miller 2009). Central regulation is likely to remain intact during acute crises, but efferent heat loss mechanisms tend to be compromised by an intense peripheral vasoconstriction due to catecholamine release (Gronert 1978). Death is prevented by removing the offending causative agent and by total body cooling. Treatment with dantrolene has also been proven to be effective in humans and swine. It is a muscle relaxant and an antipyretic, it suppresses calcium release but doesn't inhibit calcium uptake by muscles cells (Thurmon 2007).

Fever

Fever is mediated by endogenous pyrogens that increase the thermoregulatory set point. Endogenous pyrogens are released in response to exogenous pyrogens, such as infectious agents, and immune complexes, tissue inflammation or necrosis and several pharmacological agents (Miller 2005). Infections are the most common cause of perioperative fever, however other possible causes are allergic reactions, drug toxicity or anaphylactoid reactions to mis-matched blood transfusion (Kotani 1997, Rosenberg 1986). Some degree of fever could be normal after surgery, due to the inflammatory response to surgery (Frank 2000).

The treatment for fever consists of resolving the underlying cause and administration of antipyretic medications (Pernerstorfer 1999). Active cooling of the patient with fever should be performed only if the temperature reaches

dangerous values ($>41^{\circ}\text{C}$), fever being an important immune defence (Chu 1997).

2.3 TEMPERATURE DISTRIBUTION

The human body can be thought as having a core thermal compartment and a peripheral compartment (Burton 1935).

The core is constituted by trunk and head, well-perfused tissues where temperature is relatively constant and uniform. The temperatures at the different portions of the core do not differ by more than a few tenths of a degree centigrade.

The peripheral compartment is characterised by tissues with non-homogeneous and variable temperature. Physically this compartment consists of arms and legs.

Core temperatures are usually 2 to 4 $^{\circ}\text{C}$ warmer than periphery in moderate environments, and the skin surface is even cooler (Burton 1935). This difference can become larger during extreme thermal (Bristow 1994) or physiologic (Buck 1989) circumstances.

When the environmental temperature is warm or when thermoregulatory vasodilation allows an easy flow of heat from core to periphery, the core to peripheral temperature gradient is low. In contrast, vasoconstriction, due to cold environment, isolates the heat in the core compartment increasing the core to peripheral temperature gradient.

Unlike core temperature, which is strictly regulated, skin temperature can vary markedly depending on ambient exposure. Temperature of peripheral tissues depends on current exposure and exposure history, on core temperature and thermoregulatory vasomotion. Core temperature being more strictly regulated, it is the best indicator of thermal status in humans.

Heat flow

Unlike the rapid distribution of heat happening between the core tissues, heat flows relatively slowly to the periphery. Core to peripheral flow of heat is

mediated by blood borne convection and conduction of heat into adjacent tissues (Bazett 1948).

The major factors influencing convective distribution of heat are peripheral blood flow, counter-current heat exchange between adjacent arteries and veins, and the core to peripheral temperature gradient. On the other hand, the conductive component is a slower radial flow of heat from warmer tissues at the central axis to cooler tissues near the skin. Conductive flow is also determined by the diffusion coefficient, which is a function of the tissue characteristics. For example fat is a much better insulator compared to muscle (up to three time more isolative) (Anderson 1994). Hence conductive heat transfer depends mostly on intrinsic tissue characteristics rather than on thermoregulatory factors, such as vasomotion.

Heat flow is important as the heat produced by metabolism has to be dissipated to the environment to maintain thermal steady state. In humans, 95% of the heat is eliminated through the skin surface, and the remaining amount through the respiration (Bickler 1990).

2.4 THERMOREGULATION DURING GENERAL ANAESTHESIA

Almost every patient undergoing general anaesthesia will become hypothermic, generally by 1 to 3°C below normal temperature, depending on type of anaesthesia, surgical exposure and ambient temperature. Hypothermia develops with a specific pattern: temperature decreases by 1-1.5°C during the first hour after induction, followed by a slow, linear decrease in the following 2 to 3 hours and finally it reaches a steady state where it remains constant (Burton 1935) (figure 1).

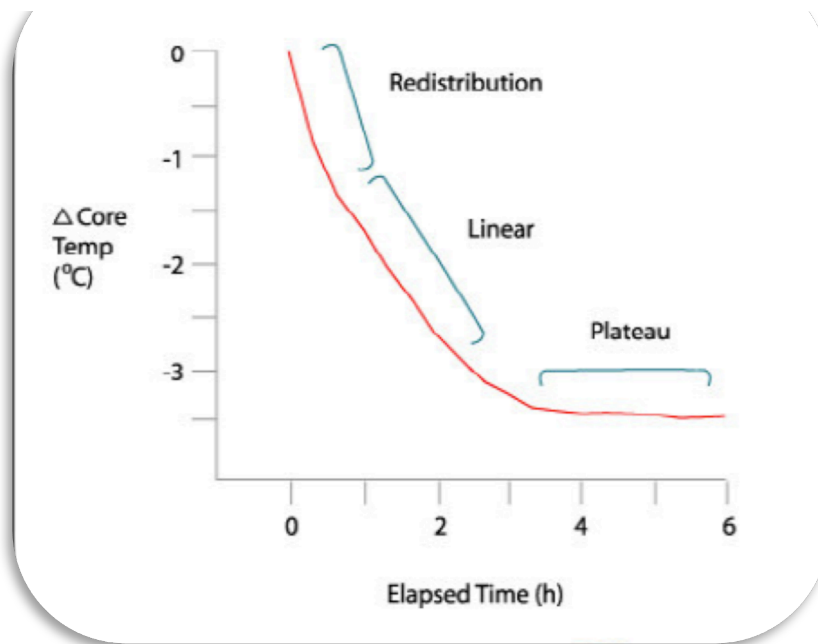


Figure 1. Core hypothermia following induction of general anaesthesia.

Each of these phases has a different explanation.

2.4.1 Redistribution

The normal core to peripheral tissue gradient is maintained by thermoregulatory vasoconstriction of arteriovenous shunts in the periphery (Rubinstein 1990).

Induction of general anaesthesia promotes vasodilation by two main mechanisms: the first one is inhibiting centrally mediated thermoregulatory vasoconstriction (Xiong 1996, Matsukawa 1995) and the second mechanism is by direct peripheral vasodilation mediated by general anaesthetics (Weiskopf 1995). Vasodilation facilitates the transit of core heat to the peripheral tissues. This internal redistribution causes a decrease in core temperature and an increase in peripheral temperature, but it does not represent a loss of heat to the environment, leaving body temperature unchanged.

In a study on human volunteers Matsukawa (1995 B) demonstrated that 1 hour after induction of general anaesthesia the temperature was decreased by 1.6°C, with redistribution contributing 81% of the decrease. In the following

two hours of anaesthesia the temperature decreased an additional 1.1°C, with a redistribution contributing only 43%. In total redistribution contributed 65% of the decrease in core temperature during the first three hours of general anaesthesia. This study showed that core to peripheral redistribution was the main cause of hypothermia during the first few hours of anaesthesia.

The severity of redistribution hypothermia is dependent by multiple factors, the most important of which is probably the patient's initial body heat content. Because heat flow needs a temperature gradient, redistribution magnitude is limited when peripheral and core temperature are similar (Just 1993).

Another important factor is the patient's fat content. Obese patients redistribute heat less compared to normal and thin patients that tend to redistribute more. This happens because obese patients, being well insulated, are generally vasodilated to try to disperse their metabolic heat. The result is that their peripheral tissue temperature is higher than normal, which reduces the core to peripheral flow of heat during anaesthesia (Kurz 1995).

2.4.2 Linear phase

The second phase of the hypothermia curve is characterized by a slow linear decrease in core temperature due to the higher heat loss compared to metabolic heat production. The metabolic rate in the anaesthetized patient is reduced by 15-40%, the main cause of this reduction is reduced brain metabolism; heat loss is also exacerbated in patients mechanically ventilated as the diaphragm and chest wall muscles are spared (Matsukawa 1995 B).

The linear phase is the phase where factors altering the heat loss are most influential and is the phase in which intraoperative heating is most effective (Hynson 1992). Cutaneous heat loss is mediated by radiation, conduction, convection and evaporation.

Radiation

Radiation is the transfer of heat from one to another surface via photons, therefore is not dependent on the temperature of the intervening air. Heat from core body tissues diffuse to subcutaneous tissues, where is lost to the environment through radiation. This is the mechanism that contributes most to the heat loss, accounting about 60% of the total heat loss in surgical patients

(Hardy 1941, Diaz 2010). The amount of heat loss by radiation is a function of the emissivity of the two surfaces and the difference between the fourth power of their temperature (degrees Kelvin). Emissivity defines an object's ability to absorb and emit heat; these two effects are always identical, otherwise objects would continue to absorb or lose heat indefinitely. Objects that absorb and emit heat perfectly are called "black bodies" and have an emissivity of one. On the other hand, perfect mirrors have an emissivity of zero. Human skin, independently of the colour, acts similarly to a black body having an emissivity of 0.95 for infrared light.

This manner of heat loss is the basis of the technology used to sense and identify the locations of persons in buildings that are out of normal view.

Conduction and convection

These two types of heat loss share a common mechanism. Conduction is the transfer of heat between adjacent surfaces. It refers to the loss of kinetic energy from molecular motion in skin tissues to surrounding air. In this case, heat transfer is proportional to the difference of temperature between the two surfaces and is dependent on any insulation between them. Water absorbs a lot more conducted heat than air, and this account for rapid hypothermia in wet patients, as well as the efficacy of water baths to cool hyperthermic patients.

Convection is the second most important cause of heat loss during anaesthesia, and is characterized by the heat loss between the skin and the layer of air surrounding it. Air movement reduces the build up of heat near the skin surface by displacing warm air with cooler air. This accounts for the cooling effect of wind and laminar air flow in many surgical suites. Conduction and convection participate to about 15% of body heat loss (Diaz 2010).

Evaporation

Evaporative heat loss is derived from the heat of vaporization of water, which is about 0.58 kcal/g. Under general anaesthesia evaporative loss occurs through the skin, respiratory tract and surgical incision. The skin evaporative losses are small, especially in animals well insulated by fur. Evaporation of

skin-preparation solutions may contribute markedly to hypothermia, in particular if alcohol-based solutions are used (Sessler 1993 B).

Respiratory evaporative losses are also small, in humans they account less than 10% of the basal metabolic rate (Bickler 1990).

Within surgical incision there is a substantial heat loss, dependent on the extent of the surgery. It has been shown that approximately half of the total heat loss is evaporative in rabbits with large abdominal incisions (Roe 1971).

Radiation	Transfer of heat from one surface to another via photons independently from the temperature of the intervening air.
Convection	Movement of cool air displacing warm air from the skin proximity
Conduction	Direct transfer of heat from one surface to an adjacent one
Evaporation	Heat loss when moisture dissipates into the air

Table n 1. Routes of heat loss during the second phase of perioperative hypothermia

2.4.3 Core temperature plateau

This is the final phase, which usually develops after 2-4 hours of anaesthesia. The core temperature tends to stabilize and remain constant. The core temperature plateau can be passively or actively maintained.

The passive plateau results when metabolic heat production matches heat loss, and no thermoregulatory defences are active. Under general anaesthesia this phase is influenced by a decreased metabolic heat production (Matsukawa 1995 B), an increased heat loss due to cold operating rooms, administration of cool intravenous fluids and evaporative and radiative losses from within the surgical incision (Roe 1971). Furthermore behavioural responses and autonomic regulation are suppressed (Xiong 1996). At constant ambient temperature, each degree reduction in core temperature reduces heat loss by about 10%. Metabolic heat production also decreases

passively, but at a slightly lower rate: 6% per each degree centigrade (Hynson 1993 B). Patients whose become sufficiently hypothermic will eventually reach a passive core temperature plateau when heat loss decreases to the point that it equals heat production. In normothermic surgical patients a passive plateau rarely develops.

The passive plateau is most common during small operations in patients that are well covered and insulated. The effectiveness of insulation is extremely important as ambient temperature and insulation are playing a primary role in heat loss (Sessler 1991).

The active plateau develops in patients where the hypothermia triggers thermoregulatory vasoconstriction. The difference between a passive plateau and an active one is that this last one depends on vasoconstriction to decrease heat loss and to alter heat distribution within the body. In this regard, core temperature is maintained much as it is normally.

Under general anaesthesia a temperature of 34-35°C is necessary to trigger thermoregulatory vasoconstriction (Matsukawa 1995, Xiong 1996); once triggered, vasoconstriction is effective largely via an unexpected mechanism. Vasoconstriction only slightly decreases cutaneous heat loss because it is largely restricted to arteriovenous shunts in the fingers and toes (Hales 1985). In contrast shunt vasoconstriction has an important influence on the distribution of body heat.

Body heat is generated by metabolic active organs in the core thermal compartment. Tonic thermoregulatory vasoconstriction tends to partially isolate a portion of that heat in the core compartment, producing the normal 3-4°C core to peripheral temperature gradient. As already discussed, general anaesthesia inhibits constriction, which allows heat to flow from core to peripheral tissues. Once in the periphery, heat cannot return to the core as it travels down a temperature gradient following the Second Law of Thermodynamics. Re-emergence of vasoconstriction therefore cannot recover heat already lost to peripheral tissues. However it restricts further flow of heat from the core to the peripheral tissues. The major effect of vasoconstriction is that the core remains relatively warmer than might be expected based on systemic heat balance. Typically, this produces a core temperature plateau (Joris 1994). Depending on the ambient temperature and on the size of the

operation, it may be manifested as a slowing in the core cooling rate or even an increase in core temperature (Bissonnette 1992).

Peripheral tissues, however, are badly affected by the thermoregulatory vasoconstriction. Not only does cutaneous heat loss continue almost unchanged (Sessler 1990), but also less heat flows peripherally from the core; the result is that peripheral tissues gradually cool. Eventually this reduction in temperature will reduce cutaneous heat loss. The major clinical implications of this mechanism is that an actively maintained core temperature plateau is typically not a thermal steady state. Instead, body heat content and mean body temperature continue to decrease.

Intraoperative	Postoperative
Clipping and prepping surgical area	Low room temperature in recovery area
Low room temperature	Lack of postoperative warming devices or insulation
Lack of warming devices or insulation	Decreased activity
Effects of drugs on body temperature	Drugs residual effects
Prolonged anaesthetic time	
Cold surface on operating table	
Cold anaesthetic gases	
Cold fluids	

Table 2. Common causes of perioperative hypothermia

2.5 CONSIDERATIONS IN PEDIATRIC PATIENTS

Infants tend to have relatively globular bodies with larger fraction of their mass in the torso compared with adults. For this reason, redistribution seems to contribute less to the initial hypothermia after the induction of anaesthesia (Bissonnette 1992).

Probably infants redistribute less because their small extremities cannot absorb as much heat from the core as in adults. Furthermore, the head constitute a far larger fraction of the total surface area, and heat loss from the head may be proportionately a larger fraction of the total. This could also be

exacerbated by the thin skull and scalp, which allow the loss of heat from the brain (Rudelstorfer 1991).

Cutaneous heat loss is proportional to surface area, whereas metabolic heat production is a function of mass. Consequently, infants easily lose large amount of heat through the skin surface (Simbruner 1985), and heat loss can easily exceed metabolic heat production (Anttonen 1995). The linear hypothermia phase is usually rapid in infants because of their high surface area to weight ratio. In contrast, respiratory losses and vasoconstriction threshold are similar to that in adults, and once constricted, an effective core temperature plateau develops also in infants (Bissonnette 1992).

Similar considerations are valid for small animals as greater degrees of hypothermia are usually attributed to smaller patients. It has been shown that oesophageal temperature of small cats (1.2 kg) tends to decrease during cooling, but also increase during rewarming at a faster rate compared to the temperature of bigger cats (3.3 kg) (Haskins 1981).

2.6 CONSIDERATIONS IN ELDERLY PATIENTS

Elderly patients become more easily hypothermic compared to younger patients probably due to impaired thermoregulatory control. They have been shown to become more hypothermic during surgery (Frank 1992), to have a decreased shivering during spinal anaesthesia (Vassilieff 1995) and after general anaesthesia and to take longer to return to normothermia postoperatively, compared to younger patients (Vaughan 1981). It has been demonstrated that elderly patients (aged between 60-80 years) compared to adult patients (aged between 30-50 years) have a reduced vasoconstriction threshold of approximately 1°C during both nitrous oxide/isoflurane anaesthesia (Kurz 1993) and nitrous oxide/sevoflurane anaesthesia (Ozaki 1997).

Impaired thermoregulatory vasoconstriction is only one factor that influences temperature regulation in elderly people. Other influencing factors are a frail constitution, reduced metabolic rate and a reduced subcutaneous fat layer (Ozaki 1997).

2.7 DRUG INFLUENCES ON THERMOREGULATION

Causes of inadvertent hypothermia include not only patient exposure to a cold environment and the inhibited behavioural responses, but the tendency of anaesthetics to promote heat loss.

Most inhalational and intravenous anaesthetic agents inhibit central thermoregulatory control, thus causing vasodilation (Diaz 2010). The vasodilative effect is summed to a direct impairment of hypothalamic thermoregulation in a dose dependent manner. Propofol (Matsukawa 1995), alfentanil (Kurz 1995 B), dexmedetomidine (Talke 1997), isoflurane (Xiong 1997), and desflurane (Annadata 1995) tend to not increase the sweating threshold, leaving the warm defences well preserved under general anaesthesia. Unlike the sweating threshold, propofol (Matsukawa 1995), alfentanil (Kurz 1995) and dexmedetomidine (Talke 1997), isoflurane (Xiong 1996) and desflurane (Annadata 1995) produce a marked decrease in the vasoconstriction and shivering thresholds favouring hypothermia development. Furthermore, the gain and maximum intensity of sweating remain normal during isoflurane (Washington 1993) and enflurane anaesthesia. However the gain of arterio-venous shunt vasoconstriction is reduced by about three times even though the maximum vasoconstriction intensity remains the same (Sessler 1992). This means that during volatile anaesthesia the vasoconstriction threshold is not only markedly decreased, but, once triggered, a three-fold degree of hypothermia is needed to obtain maximal vasoconstriction. When the maximum intensity is reached, it will prevent further core hypothermia.

Stoen (1990) demonstrated that isoflurane produces a dose dependent lowering of the threshold for thermoregulatory vasoconstriction. The dose dependent curve is approximately linear up to 1.5 MAC and the thermoregulatory threshold decreased by about 3°C/% isoflurane concentration.

Nitrous oxide depresses thermoregulation to a lesser extent compared to equipotent doses of other inhalational agents, and midazolam has minimal or no influence (Ozaki 1995, Sessler 2005).

Opioids also depress the sympathetic outflow, which further inhibits thermoregulation. In this case, the depression of the hypothalamus results in an elevated threshold for heat response, along with a decreased threshold for cold response. Therefore opioids widen the normal interthreshold range from about 0.2°C to 4 °C (Diaz 2010).

Propofol differs from sevoflurane by producing a more substantial peripheral vasodilation (Bently 1989). The effect of these two drugs on body temperature has been compared (Ikeda 1999). Core temperature in patients that were induced with propofol was significantly lower than those in patients who were induced with sevoflurane. In both groups anaesthesia was maintained with sevoflurane, suggesting that even a brief period of vasodilation, such as at anaesthetic induction, may have a substantial and prolonged effect on body temperature.

Jeong (2012) compared the effect on body temperature of two different propofol formulations: lipid-emulsion propofol and micro-emulsion propofol versus sevoflurane anaesthesia. The body temperature in the propofol lipid-emulsion group was significantly higher compared to propofol micro-emulsion and sevoflurane. The authors attribute this difference to the different metabolism of each propofol formulation. As lipid oxidation can influence the muscular thermogenesis, this could be a source of heat production. Yet, it is not clear if the amount of lipids contained in propofol lipid-emulsion is enough to produce heat and if this is the real cause of increased body temperature.

In cats, Haskins (1981) did not find a difference in decrease in oesophageal temperature between meperidine, ketamine, thiamylal, halothane and methoxyflurane.

Ketamine is unique among anaesthetics as may increase peripheral arteriolar resistance (Bidway 1975). Temperature change following ketamine induction has been compared with propofol induction, resulting in significantly greater temperatures in the ketamine group. This, again, suggests maintaining vasoconstriction during induction of anaesthesia reduces the magnitude of redistribution hypothermia (Ikeda 2001). In the same way as ketamine, phenylephrine administration, a pure α adrenergic agonist, reduced

anaesthetic induced core to peripheral redistribution of body heat, maintaining precapillary vasoconstriction (Ikeda 1999).

Shitara et al. (1996) investigated the effect of a dobutamine infusion on isoflurane anaesthetized human volunteers. This study showed a greater reduction in core temperature in patients receiving dobutamine infusion (4 $\mu\text{g}/\text{kg}/\text{min}$) compared to control. The authors attribute the result to two main factors. First, stimulation of peripheral β adrenergic receptors by dobutamine tends to produce vasodilation. In addition, the inotropic effect causes an increased blood flow to the extremities, incrementing the heat flow from core to periphery. Cutaneous heat loss may be the second factor, as it is determined by the difference between skin and ambient temperatures. As skin temperature is determined by ambient temperature, cutaneous blood flow and other factors (Hales 1985), dobutamine presumably increased cutaneous heat loss because of its vasodilatative effect.

Regional anaesthesia also produces hypothermia, with a similar pattern of heat loss produced by general anaesthesia. In humans hypothermia is very common following spinal and epidural anaesthesia. The block of afferent fibres from large body areas prevents cold input to the hypothalamus. Locally injected anaesthetics do not act directly on the hypothalamus, but nevertheless the thermoregulatory centre becomes impaired. For mechanisms not completely understood, the thermoregulatory centre incorrectly judges skin temperature in blocked regions to be abnormally elevated (Sessler 1997). The result is that the interthreshold range increases 3 to 4 times (from 0.2°C to 0.8°C). Despite this drop in body temperature patients usually feel warm because of the hypothalamic misinterpretation of skin temperature. In fact, patient may become hypothermic enough to start shivering despite their feeling of warmth (Diaz 2010).

In the present study animals were premedicated with acepromazine and buprenorphine. Acepromazine is a phenothiazine with sedative and some muscle relaxation effects. Its action is mediated by α_1 receptor blockade. Acepromazine administration produces dramatic effects on the cardiovascular system due to vasodilation. The effect of acepromazine on body temperature

is mainly due to the combination of sedation and vasodilation, which may cause a decrease in temperature (Lemke 2007).

Buprenorphine is a semisynthetic, highly lipophilic opioid. It is considered to be a partial agonist at μ opioid receptors and has long lasting analgesic effects. As all opioids, buprenorphine affects the hypothalamic regulatory system. Hypothermia tends to be the most common response, especially if opioids are associated with other sedatives or anaesthetic drugs (Gutstein 2001). Under some circumstances opioids administration causes hyperthermia in cats, horses, swine and ruminants. Part of this increase in body temperature could be attributed to increased muscle activity due to central nervous system excitation after opioid administration; however a central hypothalamic mechanism has also been implicated, but remains poorly understood (Branson 2001). Panting is also seen after opioids administration, mainly in dogs, but this effect tends to decrease with the onset of hypothermia.

To summarize, sweating is the thermoregulatory defence in humans that is best preserved during general anaesthesia. In contrast, the thresholds for vasoconstriction and shivering are markedly reduced and once activated these responses are less effective than normal.

It is intuitive to state that patients under general anaesthesia become hypothermic because they are exposed to a cold environment, cold surfaces, not always covered and insulated, they are exposed to cold fluids that are allowed to evaporate, they lose heat from surgical incision and their metabolic rate is decreased. However, the combination of all these factors would rarely produce hypothermia in a subject with intact thermoregulatory defences. Anaesthetic-induced thermoregulatory impairment is by far the most important cause of perioperative hypothermia (Sessler 2008).

Body temperature should be monitored in all patients undergoing general anaesthesia for more than 30 minutes. Monitoring body temperature and maintain normothermia is the standard of care during general anaesthesia, especially in major surgeries and in small patients where the risk of hypothermia is elevated.

2.8 TEMPERATURE MONITORING

Core temperature monitoring (tympanic membrane, pulmonary artery, distal oesophagus and nasopharynx) is used to monitor intraoperative hypothermia or to prevent overheating. Because these sites are not always convenient a variety of “near core” sites are also used clinically. These include the mouth, axilla, bladder, rectum and skin surface. Each has distinct limitations but can be used clinically in appropriate circumstances.

Common monitor sites for core temperature

Oesophagus - Multiple clinical and experimental studies, both in humans (Whitby 1968, 1971) and in animals (Shanks 1974) have shown oesophageal temperature to be reliable as indicator of mean body heat content. Oesophageal probes should be positioned at the level of the heart or even more distally to provide accurate readings (Kaufman 1987).

Tympanic membrane - The use of tympanic thermometers carries little risk of perforating the membrane, although it is possible to push a bolus of wax onto the tympanic membrane. Furthermore, it is not very easy to insert tympanic probes because of the length and angle of the ear canal and it is easy to mistake the bend of the canal for the tympanic membrane. Once properly positioned it is good practise to occlude the ear canal with cotton balls to prevent air currents from cooling the thermometer. Due to the anatomic characteristics of the external ear canal in small animal patients, tympanic membrane temperature is not an accurate temperature measurement site. In cats tympanic membrane temperature measurement was not accurate compared to rectal and oesophageal temperature (Machon 1999).

Nasopharynx - Nasopharyngeal probes should be inserted at least few cm past the nares to obtain core temperature and the patient should not breathe through the nose.

Rectum - Rectal temperature can correlate well with core temperature, but fails in accuracy during malignant hyperthermia crisis, heat stroke or quick cooling. The presence of faeces may also give a lower temperature reading (Bissonnette 1989, Cork 1983, Iuzzo 1996).

A study comparing, nasopharyngeal, oesophageal, rectal, bladder, axillar and forehead temperatures with tympanic membrane temperature, in humans, showed that nasopharyngeal, oesophageal and bladder temperature were providing the best combination of precision and accuracy (Cork 1983). Interest in monitoring tympanic membrane temperature arose, in the past, as it was thought that hypothalamic temperature was to be considered true core temperature being the hypothalamus the centre for temperature regulation (Benzinger 1969). However, because it is now recognised that thermoregulatory responses are determined by integrated thermal inputs from all body tissues, tympanic membrane temperature is no longer believed to be superior to oesophageal or rectal temperatures (Bissonnette 1991).

Mean skin temperature is the area weighted average temperature of the skin surface. Mean skin temperature is important for at least three reasons. First, the cutaneous heat loss is a function of mean-skin and ambient temperatures. Second, the central thermoregulatory control is determined by both core and mean skin temperature; and last the combination of core and skin temperatures can be used to estimate mean body temperature and therefore body heat content.

Mean body temperature it is determined by integrating the difference between heat production by metabolism and cutaneous heat loss (Belani 1993).

In 1935 Burton proposed a formula to calculate the mean body temperature:
 $MBT = \alpha \cdot \text{Core Temperature} + (1-\alpha) \cdot \text{Skin Temperature}$. This equation was based on the idea that core tissues temperature is relatively homogeneous, whereas peripheral temperature decreases parabolically going from core to skin. " α " is a coefficient that describes the contribution of core temperature to

mean body temperature. It was estimated by measuring the change in body heat content (in a calorimeter), core temperature and mean skin temperature. The resulting value was 0.64, thus $MBT = 0.64 \cdot \text{Core Temperature} + 0.36 \cdot \text{Skin Temperature}$ (Burton 1935).

2.9 COMPLICATIONS OF PERIOPERATIVE HYPOTHERMIA

A survey conducted in Europe by the TEMMP group (Thermoregulation in Europe, Monitoring and Managing Patient Temperature) in 2004 showed that central temperature is rarely monitored: in a total of 8083 surgical patients only 19.4% underwent temperature monitoring, while active patient warming was applied in 38.5% of the cases. Body temperature was registered in 25% of patients undergoing general anaesthesia, and only 6% of patients receiving regional anaesthesia (Torossian 2007). These findings showed that intraoperative temperature monitor in humans is still not a common practice in Europe and active warming is not a standard of care.

Several studies have shown the immediate and delayed consequences of mild intraoperative hypothermia on organ function, such as excessive sympathetic stimulation (Carli 1992, Frank 1995), interference with drug metabolism (Heier 1991), alteration of platelet activity (Valeri 1987), inhibition of immune system and impaired wound healing (Sheffield 1994), increased postoperative break down of muscle proteins (Carli 1989, 1991). According to Slotman (1985) prolonged postoperative hypothermia was associated with increased mortality.

Cardiovascular complications

Several studies demonstrated how mild hypothermia favours the occurrence of tachycardia, hypertension, systemic vasoconstriction and an imbalance between myocardial oxygen demand and supply due to an increase in level of circulating catecholamine (Frank 1993, 1995).

As body temperature falls and the sino-atrial node cools, both heart rate and arterial blood pressure fall, and there is a greater risk of cardiac arrest as myocardial irritability increases. As the temperature decreases, the ECG

morphology changes, QRS intervals become prolonged, depression of the ST segment appears and T wave may invert. These changes signify a gradual breaking up of the conduction, until eventually the complexes are unrecognisable. Once the zone of myocardial irritability has been reached (below 30 °C), ventricular fibrillation or asystole can occur at any moment, though it seems that in smaller and younger animals the temperature at which it occurs tends to be lower (Churchill-Davidson 1956).

Below 30° the oxygen requirement drops by about 50% and heart rate and cardiac output are decreased by 35% and 40% respectively. This cause a decrease in arterial blood pressure of 60%. Although the oxygen requirement is decreased, the delivery is not sufficient to maintain aerobic metabolism and anaerobic metabolism and lactic acidosis occur. In addition, there is a shift of fluids from the vascular bed to the interstitial space, which results in haemoconcentration and a tendency to erythrocytes sequestration and sludging as the temperature approaches 26 °C (Manohar 1972). The blood viscosity can increase up to 200% and when body temperature reaches 22-23°C ventricular fibrillation and death may occur (Haskins 2007).

Frank et al (1993, 1997) also showed a higher prevalence in myocardial ischemia, postoperative angina and decreased arterial partial pressure of oxygen in hypothermic human patients undergoing lower extremity vascular surgery, compared to normothermic patients. With a temperature of 1.3°C below the physiological ranges patients were three time more likely to develop adverse myocardial outcomes.

Hypothermia may also cause a left shift in the oxygen-haemoglobin dissociation curve, resulting in decreased off loading of oxygen to the tissues and local hypoxia or dysoxia (Cabell 1997, Yoshida 2001).

Cardiovascular changes can also be associated with detrimental renal effects. Mild to moderate hypothermia may cause a cold diuresis because of increase in glomerular filtration rate, vasoconstriction and decreased response to antidiuretic hormone. Severe hypothermia could lead to decreased renal blood flow, decreased glomerular filtration rate, blood sludging, ischemia or cold renal tubular damage, and ultimately in acute renal tubular necrosis (Reuler 1978).

It is important to remember that aggressive rewarming of severely hypothermic patients should be avoided because peripheral vasodilation may induce excessive hypotension. Furthermore, ischemic peripheral tissues may accumulate metabolites that could have deleterious cardiovascular effects once they are introduced in the systemic circulation. It is suggested that the rewarming should not exceed 1°C/hour (Danzl 1988).

Haemorrhagic complications

Hypothermia seems to increase blood losses during surgical procedure because of impaired platelet and clotting factors function. Higher haemorrhagic risk was demonstrated for patients undergoing colo-rectal and hip replacement surgery, where hypothermic patients were more likely to receive a blood transfusion compared to normothermic individuals (Kurz 1996, Schmied 1996). Winkler (2000) showed how a reduction in central temperature of 0.5°C may increase surgical blood losses. Other evidence confirmed lower intraoperative blood loss, decreased need of blood products and shorter hospitalization time in patients actively warmed during anaesthesia compared to controls. Furthermore, maintenance of normothermia reduced the total costs for anaesthetic treatment by 24% during major abdominal surgery (Bock 1998).

Infectious complications

Hypothermia as a risk factor for wound infection is, at the moment, a debatable subject.

Hypothermia may increase the risk of wound infection by two mechanisms: the first mechanism is related to the hypothermia-induced vasoconstriction which cause a decrease of subcutaneous oxygen tension (Sheffield 1997), that has been shown to correlate with an increased incidence of surgical wound infection (Hopf 1997).

The second mechanism is an inhibitory effect on the immune system by decreasing circulating white blood cells, impairing the release of white blood cells from the bone marrow, slowing the clearance of bacteria from the systemic circulation and impairing phagocytosis (Biggar 1983). Furthermore, anaesthesia as well could affect the immune response by extrinsic

contamination of anaesthetic drugs (Heldmann 1999, Veber 1994), inhibition or stimulation of cytokines release, increased number of CD8+ suppressor/cytotoxic lymphocytes and impairment of chemotactic, phagocytic and oxidative function (Brand 1997).

Kurz (1996) reported an increase in infection risk (three times more) in human patients undergoing colorectal surgery that developed a mild perioperative hypothermia compared to normothermic patients. In this study hypothermia was also associated with a delayed wound healing and prolonged hospitalization. A more recent study (Melling 2001) confirmed a reduced wound infection risk in patients both systemically and locally pre-warmed. Thirty minutes of warming, before surgery, reduced infections rate from 14% in non pre-warmed patients, to 5%.

Differently, Munn (1998) found no relationship between hypothermia and wound infection in women undergoing caesarean section. Another veterinary retrospective study (Beal 2000) with more than 700 dogs and cats, showed that perioperative temperature was not associated with infection rate. In this study the duration of anaesthesia was significantly associated with increased risk of clean wound infection.

Decreased drug metabolism

Central temperature can markedly affect the pharmacokinetic and pharmacodynamic properties of several drugs. At low body temperature drug metabolism is compromised and this is of particular interest during general anaesthesia. Body temperatures between 32-34°C are associated with reduced anaesthetic requirements and a prolonged recovery time. When the temperature decreases to 28-30°C the central nervous system (CNS) becomes markedly depressed and usually no anaesthetic agent is required (Eger 1965).

The minimum alveolar concentration of volatile agents is reduced as well. Regan and Eger (1967) found that MAC for both halothane and methoxyflurane at 28°C was 50% of normothermic values.

Decreasing drug elimination, nerve conduction and muscle contraction, hypothermia can also markedly influence the use of neuromuscular blocking agents and doses may need to be reduced to prevent prolonged paralysis

(Martinez 2007). Heier (1991) demonstrated how a 2°C reduction in core temperature doubled the duration of effect of vecuronium in humans, and atracurium was shown to have a prolonged duration of action by 60% by a reduction in core temperature of 3 °C (Leslie 1995).

During a constant infusion of propofol, plasma concentration is increased by 30% in patients who are 3°C hypothermic (Leslie 1995).

The delay in hepatic degradation of drugs can set up a vicious circle of prolonged heat loss and delayed recovery. Delayed recovery is not surprising as mild hypothermia increases anaesthetic potency, decreases drug metabolism, reduces cognitive performance and is associated with cardiovascular instability. Lenhardt (1997) showed that 2°C intraoperative core hypothermia per se prolonged post-anaesthetic recovery by about 40 minutes in human patients undergoing major abdominal surgeries. Another study, in dogs, demonstrated an association between decreasing body temperature and prolonged recovery (Pottie 2007). If hypothermia is unrecognized, excessive anaesthetization and hypoventilation may cause unnecessary mortality (Dale 1968).

Deleterious effects of hypothermia
Cardiac arrhythmias and ischemia
Increased peripheral vascular resistance
Left shift of the haemoglobin-oxygen dissociation curve
Platelet dysfunction
Postoperative stress response
Altered mental status
Impaired renal function
Decreased drug metabolism
Decreased wound healing
Increase incidence of infection

Table 3. Deleterious effects of hypothermia

Although hypothermia is generally regarded as deleterious, it can be beneficial in some situations. Hypothermia decreases metabolic rate by 8% per °C to about half the normal rate at 28°C (Sessler 2005), for this reason oxygen demand and consumption drop. This allow aerobic metabolism to continue during periods of compromised oxygen supply, therefore reducing the production of anaerobic byproducts such as superoxide radicals and lactate. An additional protective function can be ascribed to the decreased release of excitatory neurotransmitters, kinases and proinflammatory cytokines and decreased apoptosis (Coulborne 1997). Furthermore, hypothermia lowers intracranial pressure and cerebral perfusion pressure (Sessler 2005). Substantial protection against cerebral ischemia and hypoxia is obtained by decreasing the body core temperature of 1 to 3°C. Therapeutic hypothermia is common practice during several neurosurgery cases and coronary artery bypass surgery. It has also been shown to improve outcome during recovery from cardiac arrest (Bernard 2002).

As in humans, hypothermia in dogs has been shown to have beneficial effects in protecting the brain from ischemia during resuscitation without impairing cardiovascular recovery. However, the detrimental cardiovascular effects of moderate hypothermia outweighed the neurologic benefits (Weinrauch 1992).

2.10 PREVENTION AND TREATMENT OF HYPOTHERMIA

Hypothermia can cause severe discomfort in the conscious patient. Recovery becomes prolonged not only because of the delayed awakening due to altered mentation, but also due to the decreased drug metabolism. These factors are added to the negative physiological influences addressed previously. As with most anaesthetic complications, prevention is the best strategy. This can be achieved to some extent by pre-warming the patient's skin surface before induction of anaesthesia (Just 1993), or warming the inner or outer parts of the body throughout the course of anaesthesia and surgery (Frank 1993).

The main cause of heat loss after induction of anaesthesia is the redistribution of heat from the core to the periphery of the body. The amount of redistributed heat is proportional to the gradient between the two compartments, which is influenced by several factors such as room temperature, peripheral vasoconstriction/dilation and body condition.

It is difficult to treat redistribution hypothermia for two main reasons. First because the internal flow of heat is large, and second because heat applied to the skin surface requires a long time to reach the core thermal compartment. However, redistribution can be prevented by pre-warming the patient's skin surface before undergoing general anaesthesia. Cutaneous warming before induction of anaesthesia has little effect on core temperature, which remains very well regulated (Hynson 1993). It does increase peripheral tissue temperature and reduce the normal core to peripheral temperature gradient. For this reason, induction of anaesthesia produces little redistribution hypothermia because heat tends to flow down a temperature gradient. The efficacy of pre-warming is dependent on the increase in heat content in the peripheral compartment (extremities) (Sessler 1990 B, Just 1993).

Two main factors could limit the efficacy and speed of pre-warming. In humans, sweating is an effective thermoregulatory response, able to easily dissipate more heat than is provided by the best clinical warming device. Sufficiently aggressive cutaneous warming may thus trigger sweating and

reduce net cutaneous heat transfer. Sweating could be compared with panting in domestic animals, whose dissipate the excessive heat mainly by this method. A second factor is that high skin temperature, and especially a rapid increase in temperature, provokes thermal discomfort. Such discomfort may limit the tolerability of the aggressive warming (Sessler 1995).

It has been demonstrated that active pre-warming of human patients with forced-air blankets before their arrival in the operating room can minimize redistributive hypothermia during both general (Hynson 1993, Just 1993, Camus 1995, Andrezejowki 2008) and regional anaesthesia (Glosten 1993). Glosten proved that pre-warming of healthy volunteers undergoing lidocaine epidural injection for two hours raised skin temperature (but not core temperature) and helped prevent hypothermia. Hypothermia may develop after epidural anaesthesia due to the inhibition of thermoregulatory vasoconstriction by the sympathetic block. The cool periphery is then warmed at the expense of the core compartment.

These studies have applied moderate heat intensities for 1.5 to 2 hours to healthy human volunteers, but such prolonged pre-warming is often impractical in most hospitals.

During the intraoperative period heat is mainly lost through radiation and convection from the skin surface. The easiest way to decrease heat loss would be to maintain a high room temperature, which is often not applicable in operating rooms. All patients become hypothermic when the room temperature approaches 21°C. Hence the operating room should be warmed to greater than 24°C during induction and while the patient is prepared and draped. Once warming devices have been applied to the patient, the room temperature could be lowered to a comfortable range for the staff.

Also patient positioning is important, the more radially positioned are the extremities of the patient, the greater the heat loss. Other strategies include both passive insulation and active warming. Multiple studies indicate that active methods are more efficient in maintaining a perioperative normothermia (Borms 1994, Krenzischek 1995). Interestingly, active warming not only to improved thermal comfort and core temperature, but also reduced pain and improved overall patient satisfaction (Negishi 2003).

In the author's knowledge there are not many studies investigating the effect of pre-warming in small animals. Most of the veterinary studies focused on intraoperative warming. Machon et al (1999) demonstrated that body temperature of cats warmed with a forced air warming blanket during 90 minutes of anaesthesia was significantly higher compared to non-warmed cats.

Warming strategies focused on the periphery of the body are particularly effective. A trial, evaluating the efficacy of three perioperative warming protocols to improve body temperature in anaesthetised dogs, showed how peripheral warming only was more effective than single or double sided trunk warming (Cabell 1997).

There are three main warming strategies: passive insulation, active cutaneous warming and internal warming.

Passive Insulation

The principle behind passive insulation is to reduce heat loss by insulation of the air layer between cover and skin surface; the efficiency of this system is directly proportional to the area of surface covered. There are several devices to insulate the patient, including surgical draping, cotton blankets, metallized plastic covers and bubble wrap blankets.

Sessler (1993) showed that the heat loss of patients covered with cotton blankets is decreased by 33%. Increasing the number of insulating layers, as well as warming insulating blankets does not increase the efficiency of this system. However, Haskins (1981) did not find any advantage in preventing hypothermia by cocooning cats with towels or space blankets.

Active cutaneous warming systems

The goal of these methods is to increase the air temperature around the patient, thereby reducing the temperature gradient between the body surface and the environment, thus decreasing the convection and conduction heat loss.

Forced-air warming devices

These are the most active warming systems. They provide heat by convection and reduce the loss by radiation. They consist of an electrically powered heater blower unit and a paper or plastic patient cover (Borms 1994, Negishi 2003). These systems are safe and effective, if used correctly. There are reports of disconnection of the hose from the blanket, referred to as 'free hosing' resulting in hot air blowing directly onto the patient. Consequences of this can be severe, including skin necrosis (Marders 2002).

Resistive heating blankets

These are inexpensive non-disposable devices based on carbon fibre technology and use direct current. These machines can independently heat numerous cover segments and consequently a large fraction of the body surface can be warmed during almost all type of operation (Negishi 2003).

Circulating water mattresses

These devices are considered to be less effective compared to the other systems, especially in the adult patient (Hynson 1992). But they have been proven effective in maintaining body temperature in experimental cats (Haskins 1981) and in dogs and cats undergoing surgery (Evans 1973). Furthermore, circulating water is associated with "pressure-heat necrosis" that results when tissue compressed by the weight of the patient is simultaneously warmed (Gendron 1980).

Radiant warmers

These machines generate infrared radiation and have the advantage to not be in direct contact with the patient. Their efficiency depends on the distance between the device and the skin, as well as its direction. Exposure to the infrared lamp at a distance of 25 to 50 cm caused hyperaemia and excessive surface temperatures in cats. When the lamp was positioned at a distance of 100 cm from the cat, the surface temperature decreased to a point below oesophageal temperature. A distance of 75 cm was reported to be the most effective and safe position for the lamp (Haskins 1981). The main limit of

radiant warmers is that they do not prevent heat loss by convection, which is one of the main causes of hypothermia (Hynson 1992).

Negative-pressure warming

This is a newly introduced method that uses negative pressure combined with heat to facilitate warming in vasoconstricted postoperative patients. It uses negative pressure applied to one arm, which is thought to dilate the arteriovenous shunts and to increase arm blood flow. In theory, this allows rapid transfer of applied heat from the arm to the core. Initial studies showed promising results, with a 10 fold increase in the rewarming rate using negative-pressure warming devices compared to heat applied alone (Grahn 1998). However further tests failed to demonstrate the advantage of using this method compared to forced air warming, warm blankets and radiant heat (Taguchi 2001, Smith 1999).

Internal warming systems

The goal of this method is to provide heat centrally to rapidly warm the body core.

Intravenous fluid warming

Warm fluids should reduce hypothermia due to the infusion of solutions at body temperature. Although fluid warming is useful, especially if large volumes are administered, it is not an adequate method to maintain normothermia by itself and it should not be considered as an alternative to active warming of the patient.

Inspired gas warming

In the 1970s inspired gas warming and humidification have been reported to maintain and even rewarm body temperature in humans and rabbits (Marfatia 1975). Haskins and Patz (1980) designed an inspired-air warming and humidifying unit for the use in cats. Although the net body heat loss seemed reduced by the technique, it was not successful in preventing hypothermia in cats. Furthermore, high inspired-gas temperatures (40-43 °C) were

associated with a severe increased of respiratory secretion and possible tracheal lesions.

Now days, heat and moisture exchanging filters are often placed between the tracheal tube and the breathing system. Their function is to conserve the heat of the exhaled breath and use it to warm the inhaled gases, reducing losses through evaporation.

Amino acid intravenous infusion

This technique has been demonstrated to increase the metabolic heat production in human patients under general anaesthesia. Approximately 60% of the heat produced in response to amino acid administration accumulates, thus increasing the temperature of mixed venous blood (Brundin 1994). The thermic effect of amino acids was found to be increased five fold during and immediately after isoflurane-nitrous oxide anaesthesia. The enhanced thermogenesis counteracts the anaesthesia-induced reduction in metabolism and prevents the development of hypothermia (Sellden 1994, 1996).

Sellden (1998) showed that patients whose were receiving amino acids intravenously during surgery maintained a core temperature 0.5°C higher compared to patients receiving crystalloids.

Other possible warming techniques that have been described are peritoneal dialysis, arteriovenous shunt and cardiopulmonary bypass, which is the most effective system to actively warm a patient (Gentilello 1992). Obviously these systems cannot be routinely applied to prevent and treat mild perioperative hypothermia.

Complications of rewarming

It is important to realize that these warming systems, although very useful, can potentially be harmful for the patient. Complications of active warming include increased metabolic rate and oxygen consumption, mild to moderate hyperthermia and thermal burn injuries.

An American Society of Anesthesiologists closed claims study reported 54 burns among 3000 anaesthesia claims. Patient warming devices caused 28

burns, with circulating-water mattresses being responsible for 5 of them (Cheney 1994).

Burns due to warming devices have been reported also in dogs, in particularly using electric heating pads (Heavner 1978) and water filled gloves (Dunlop 1989).

Thermal injuries from warm water blankets, hot water bottles and electric blankets can be very serious. Factors affecting thermal burns include the presence of layers of padding between the device and the patient, the patient hair coat thickness and its body weight (Swaim 1989). The recommended surface interface temperature between the animal and the heating pad is 41°C – 42°C. Another important factor in the development of thermal injury is the duration of contact between patient and heating device. It is good practice to put some insulation between the two or to turn the patient regularly if the contact is prolonged (Swaim 1989).

Two additional complications of rewarming are afterdrop and rewarming shock (Oncken 2001, Sessler 2000, Reuler 1978). Afterdrop refers to a condition in which body temperature continues to decrease despite active or passive warming. Once warming is started, peripheral vasodilation occurs with the result of warm blood moving to the periphery and cooler blood returning to the core. Rewarming shock is characterised by rapid vasodilation secondary to external warming followed by venous pooling at a degree that the circulatory system cannot overcome.

2.11 POSTOPERATIVE CONSIDERATIONS

As well as during anaesthesia, the recovery phase is a delicate stage for temperature loss. Holdcroft (1978) demonstrated a large decrease in skin temperature during transfer of patients in the recovery room, despite the beginning of patient activity and maintenance of the environmental temperature. This could have been accounted for by the removal of the surgical drapes from the patient. This decrease was larger than the hourly

loss during anaesthesia and, in view of the detrimental effects of hypothermia, should be adequately prevented.

During the recovery period, the body thermal conditions change. Once the anaesthetic induced vasodilation dissipates, thermoregulatory vasoconstriction begins and the transfer of heat from the periphery to core structure is markedly impaired. For this reason the use of skin warming devices is not as effective as it is during general anaesthesia when the patient is vasodilated. Hence, it is easier to maintain intraoperative normothermia than to rewarm the patient postoperatively.

Residual hypothermia at the end of surgery commonly leads to shivering.

Human patients often describe feeling cold as one of the most unpleasant aspects of their hospitalization, sometimes worse than any pain associated with the procedure (Diaz 2010). Shivering is not only unpleasant, but is also physiologically stressful as it increases blood pressure, heart rate, oxygen consumption and catecholamine concentration. In patients that underwent surgery, it may also worsen the pain and increase stretch on surgical wounds. However, postoperative tremors are not always caused by hypothermia. Other additional causes of tremors are disinhibition of spinal reflexes, decreased sympathetic activity, pyrogens release, adrenal suppression and pain. It is important to remember that pain may be triggering tremors in normothermic patients (Horn 1999).

Skin warming devices are usually a comfort for the patient, but the skin surface contributes only 20% in the control of shivering and they are often not proven effective in patients with core temperature much below 35°C (Sessler 2005).

3. AIM OF THE STUDY

Under general anaesthesia small animals usually become hypothermic. Heat loss begins after the pre-anaesthetic medication of the animal. Pre-warming the patients in incubator in this period might help to decrease the drop in body temperature.

The objective of this study was to investigate if the pre-warming of small animals after the pre-anaesthetic medication affects temperature during general anaesthesia.

The hypothesis of this study was that pre-warming of small animals in an incubator after pre-anaesthetic medication and prior to general anaesthesia would have reduced the incidence and/or severity of hypothermia under general anaesthesia.

4. MATERIALS AND METHODS

This study was approved by the AHT Clinical Research Ethics Committee (Animal Health Trust, Newmarket, UK).

4.1 ANIMALS AND INCLUSION CRITERIA

Dogs and cats, weighing less than 10 kg, with an ASA physical status I or II, undergoing general anaesthesia for minor procedures or ocular surgeries were considered for recruitment in the study. A sample size calculation was performed following recruitment of the first ten cases. Seven cases in each group would have had an 80% power to detect a difference between mean oesophageal temperature at thirty minutes of 1°C with a significance level of 0.05.

The American Society of Anesthesiologists (ASA) has developed a scale to rate physical status. A patient is assigned to a category status from I to V. I corresponds to a normal healthy patient, and V is moribund (Table 4). This scale has been shown to be predictive of anaesthetic morbidity and mortality in veterinary patients.

ASA	Physical description
I	Normal patient, no disease
II	Mild systemic disease not limiting normal function
III	Severe systemic disease limiting normal function
IV	Severe systemic disease, constant threat to life
V	Moribund

Table 4. American Society of Anesthesiologists (ASA) scale of physical status.

After completion of a thorough physical examination and interpretation of the data from ancillary tests, an ASA physical status was assigned. Only patients ASA I or II were included in the study.

Animals were enrolled in the study if undergoing minor procedures under general anaesthesia, such as radiography, ultrasonography, endoscopy, biopsies, radiotherapy or eyelid and intraocular surgeries. Animals undergoing more invasive procedures were not enrolled in the study.

4.2 STUDY GROUPS

Data for dogs and cats were analysed separately.

All the patients were block randomized into two groups: a pre-warmed group (treatment group) and a non pre-warmed group (control group).

1. Pre-warmed group

Patients in the treatment group were placed in an incubator, with temperature set at 33°C, for a duration of 30 minutes. The pre-warming period started immediately after pre-anaesthetic medication and was followed by induction of general anaesthesia.

2. Non pre-warmed group

Patients in the control group did not receive any pre-warming after pre-anaesthetic medication.



Figure 2. Incubator

4.3 PROTOCOL

All animals were hospitalized for at least one hour before the beginning of the study.

Dogs and cats were kept in two different wards in single kennels. Kennels were provided with soft bedding and water, which was removed at the time of the pre-anaesthetic medication. Food was withheld from the previous night.

Pre-anaesthetic medication and anaesthetic protocol were standardized for all animals.

Pre-anaesthetic medication consisted of acepromazine (Calmivet® Vetoquinol, UK) 0.02 mg/kg and buprenorphine (Vetergesic® Alstoe Animal Health, UK) 0.02 mg/kg administered intramuscularly. After the pre-anaesthetic medication, animals in the pre-warming group were moved into a paediatric incubator (Dräger Incubator 8000 SC, UK) previously warmed to 33°C. Animals in the non pre-warming group were left in their kennel. An intravenous catheter (20 or 22 Gauge Jelco or Abbott Laboratories, UK) was placed in a peripheral vein before pre-anaesthetic medication if possible. In case of uncooperative animals the catheter was placed 30 minutes after pre-anaesthetic medication.

Before induction of general anaesthesia the sedation was scored with a simple descriptive scale of 1 to 5. Sedation score 1 represented a non

discernable sedation, 2 was associated with a mild sedation, 3 was moderate sedation, possible recumbence but still rousable, 4 heavy sedation, animal recumbent and difficult to rouse, 5 profound sedation, lateral recumbency and animal not rousable (Table 5).

General anaesthesia was induced with an intravenous injection of alfaxalone (Alfaxan® Vetoquinol, UK) to effect (about 2 mg/kg). Dogs and cats were oro-tracheally intubated and maintained on isoflurane (Ohmeda Isotec 4) in 100% oxygen through a Mini Lack breathing system (Burtons, UK) or a Humphrey ADE (Anaequip, UK). Oxygen flow was kept at 200 mL/kg/minute and isoflurane was vaporized at a concentration of 2% and adjusted as required. An heat and moisture exchanger (HME) (Hygrobaby Filter Nellcore or Cory Bros neonatal Filter, UK) (Figure 2) was placed between the endotracheal tube and the breathing system. Intravenous fluids (Hartmann's solution – Aqupharm 11 Animalcare, UK) were started after induction at a rate of 5 mL/kg/hour. All animals were insulated from the table surface by an incontinence pad. No additional warming systems were applied.

If analgesia was required, intravenous fentanyl citrate (Martindale Pharmaceuticals, UK) (1-3 µg/kg) was administered to effect intravenously.

Intraocular surgeries required neuromuscular blockade. In these cases, patients were mechanically ventilated (Zoovent CWC 600 AP, UK) and received atracurium besilate (Tracrium, Glaxo-Smith-Kline, UK) at a dose between 0.1 and 0.2 mg/kg intravenously. The neuromuscular block was monitored with a peripheral nerve stimulator (Innervator 252 Fisher & Paykel, Healthcare, UK).



Figure 3. On top two different size of paediatric HME. Lower, Cat anaesthetised with HME and oesophageal temperature probe in place.

Sedation score	Description
I	Non discernable sedation
II	Mild sedation
III	Moderate sedation, possible recumbence but still rousable
IV	Heavy sedation, animal recumbent and difficult to rouse
V	Profound sedation, lateral recumbency and animal not rousable

Table 5. Sedation score description

Pre-anaesthetic medication	
30 minutes in incubator	30 minutes in kennel
Induction of anaesthesia	
Temperature measurement during anaesthesia	

Table 6. Summary of study protocol

Monitoring

Baseline body temperature was recorded at the time of premedication with a digital rectal thermometer (Syrvet, US).

An oesophageal temperature probe (MEAS thermistor, US) was inserted immediately after anaesthesia induction and advanced into the oesophagus till the level of the heart. A rectal temperature probe (MEAS thermistor, US) was inserted of about 4 cm into the rectum at the same time. The two temperature probes were connected to multiparameters monitors (Mindray PM 8000 Vet US or Fukuda Denshi Dynascope US).

Ambient temperature (Digital thermometer, Brannan England UK or Burtons UK), oesophageal temperature and rectal temperature were recorded from induction, every 5 minutes, till the oesophageal temperature dropped below 36°C. At this point the study was discontinued and the patient was actively rewarmed.

During general anaesthesia the following parameters were monitored every 5 minutes: heart rate, respiratory rate, non invasive blood pressure, end-tidal carbon dioxide tension, end-tidal isoflurane when possible, arterial haemoglobin oxygen saturation, train of four when neuromuscular blocking agents were used, drugs administration.

Any shaved body area or surgical prepared area or area in contact with ultrasound gel was recorded.



Figure 4. Anaesthetised cat, lying on an incontinence pad. Oesophageal temperature probe and HME are in place.

4.4 STATISTICAL ANALYSIS

Data for cats and dogs were analysed separately. After normality testing with the D'Agostino and Pearson omnibus normality test, groups were compared using t-tests or Mann Whitney ($P < 0.05$). For the first hour of anaesthesia, temperatures were compared using ANOVA with post hoc Bonferroni correction. Fisher's exact test was used to assess the proportion of animals withdrawn because of hypothermia.

5. RESULTS

A total of forty seven client owned animals were enrolled in the study. Of these animals, twenty two were dogs and twenty five were cats. Ten dogs were male neutered, two male entire, nine female neutered and one female entire. Twelve cats were male neutered, one was male entire. Eleven cats were female neutered and one was entire. Two cats participated twice in the study.

The distribution of breeds are shown in table 5 for dogs and cats.

Dog's breeds	Number of animals per breed	Cat's breeds	Number of animals per breed
Cross breed	3	Domestic short hair	18
Jack Russell Terrier	4	Domestic long hair	3
Bichon frise	3	British short hair	1
Yorkshire terrier	2	Siamese	2
Pug	4	Burmese	1
West Highland White Terrier	3		
Chihuahua	2		
Miniature schnauzer	1		

Table 5. Breeds and numbers of animals each breed present in the study.

Thirteen cats and ten dogs were pre-warmed, twelve cats and nine dogs were controls. Three dogs in the pre-warming group were excluded from the study as they became excessively stressed while in the incubator. No cats showed distress while in the incubator.



Figure 5. Cavalier King Charles Spaniel in incubator

Overall the mean weight in dogs was 7.3 ± 2.4 kg and in cats 4.4 ± 0.9 kg.

Mean age of dogs was 72.6 ± 44.9 months and of cats was 70.6 ± 46.6 months.

Median body condition score was 6 (4-7) in dogs and 6 (4-8) in cats.

Median sedation score was 2 (1-3) in dogs and the same for cats.

Time in incubator was 30.5 ± 0.5 minutes in dogs and 30 ± 0 minutes in cats.

Time spent out of incubator before induction was 23 ± 12.5 minutes in dogs and 19.6 ± 7.2 minutes in cats.

Time from sedation to induction of general anaesthesia was 56.3 ± 22.5 minutes in dogs and 49.7 ± 12.5 minutes in cats.

Duration of anaesthesia was 95.1 ± 46.8 minutes in dogs and 74.6 ± 46.0 minutes in cats.

There were no differences between groups for age, weight, BCS, sedation score, time in the incubator, time from sedation to induction or duration of anaesthesia (Table n. 6).

	Dogs			Cats		
	Control	Pre-warmed	P value	Control	Pre-warmed	P value
Weight (kg)	7.0 ± 1.7	7.3 ± 3.0	0.9	4.3 ± 0.9	4.4 ± 1.0	0.56
Age (months)	76.4 ± 44.2	69.2 ± 50.0	0.75	68.0 ± 38.0	73.0 ± 54.9	0.80
BCS (median and range)	6 (5-7)	5.5 (4-7)	0.21	5.5 (4-8)	6 (3-7)	0.72
Sedation score (median and range)	2 (1-3)	2 (2-3)	0.26	2 (1-2)	1 (1-3)	0.15
Time sedation-induction (minutes)	59.4 ± 29.2	53.5 ± 15.6	1	50 ± 16.9	49.6 ± 7.2	0.21
Time in incubator (minutes)	0	30.5 ± 5.5	-	0	30 ± 0	-
Time out of incubator (minutes)		23 ± 12.5	-		19.6 ± 7.2	-
Duration of anaesthesia (minutes)	80.3 ± 31.5	108.5 ± 55.6	0.39	70.4 ± 34.0	78.4 ± 55.9	0.85

Table 6. Comparison of study data (mean ± standard deviation) or (median & range).

The animals participating in the study were anaesthetised for the following procedures: radiography and ultrasonography, neuromuscular investigations including electromyography and nerve conduction velocity; bone marrow biopsy, radiotherapy with Strontium 90, lymph nodes removal, liver tru-cut

biopsy, nasal biopsy, upper gastrointestinal endoscopy, keratectomy, eyelids surgery (entropion correction, cryosurgery for dystichiasis removal), cataract surgery, retinopexy, endoscopic cytophotocoagulation (ECP) and tissue plasminogen activator (TPA) intraocular injection (Table 7).

Procedure	Number of dogs	Number of cats
Imaging work up	3	10
Neuromuscular work up	1	1
Strontium 90 treatment	0	4
Lymph node removal	0	1
Liver biopsy	1	0
Endoscopy	2	0
Nasal biopsy	0	1
Bone marrow biopsy	0	1
Keratectomy	1	2
Eyelids surgery	3	3
Cataract surgery	5	1
Other intraocular surgeries (ECP, retinopexy, TPA injection)	3	1

Table 7. Number of animals undergoing each procedure

Baseline rectal temperature, taken at the time of pre-anaesthetic medication was $37.9 \pm 0.6^{\circ}\text{C}$ in dogs and $38.0 \pm 0.5^{\circ}\text{C}$ in cats. There was no difference in baseline rectal temperature between groups both in dogs ($37.8 \pm 0.6^{\circ}\text{C}$ in the control group and $38.0 \pm 0.6^{\circ}\text{C}$ in the pre-warmed group, $P = 0.52$) or cats ($38.2 \pm 0.4^{\circ}\text{C}$ in the control group and $38.0 \pm 0.6^{\circ}\text{C}$ in the pre-warmed group, $P = 0.50$).

Oesophageal and rectal temperatures at induction were similar and remained similar between groups throughout the first hour of anaesthesia. There was no difference in oesophageal and rectal temperature at induction between treatment groups for dogs and cats. There was no difference between

baseline rectal temperature and rectal temperature at induction between groups for dogs and cats. (Table 8)

	Dogs			Cats		
	Control	Pre-warmed	P value	Control	Pre-warmed	P value
Baseline rectal temperature (°C)	38.1 ± 0.6	37.8 ± 0.6	0.53	38.2 ± 0.4	38.0 ± 0.6	0.50
Oesoph. temperature at induction (°C)	37.4 ± 0.7	37.5 ± 0.4	0.32	37.8 ± 0.4	38.1 ± 0.6	0.21
Rectal temperature at induction (°C)	37.5 ± 0.8	37.3 ± 0.5	0.87	37.8 ± 0.4	38.3 ± 0.8	0.07

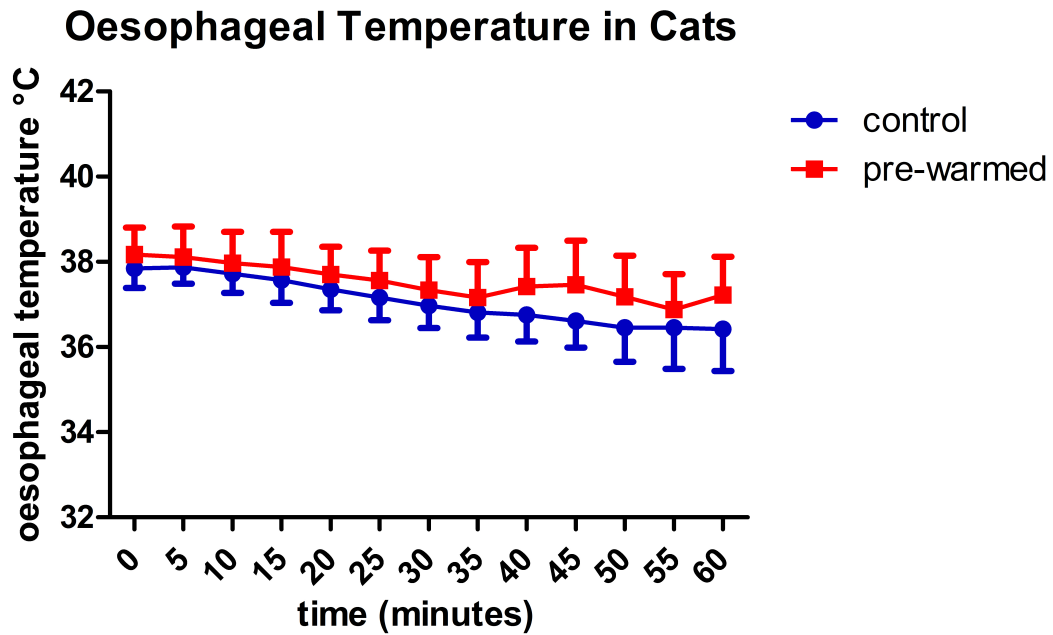
Table 8. Mean ± standard deviation base-line rectal temperature, oesophageal temperature at induction, rectal temperature at induction and oesophageal of anaesthesia in the different groups.

Oesophageal and rectal temperatures were not correlated for cats ($r = 0.03394$, $P = 0.635$). Differently, for dogs there was a correlation between oesophageal and rectal temperature (these were non-parametric data sets) (Spearman, $r = 0.2335$, $P = 0.0017$).

Seven out of ten dogs in the pre-warmed group, were withdrawn from the study, due to temperature decrease below 36°C, and five of nine dogs in the control group. In cats, two of thirteen were withdrawn from the pre-warmed group and five out of twelve in the control group.

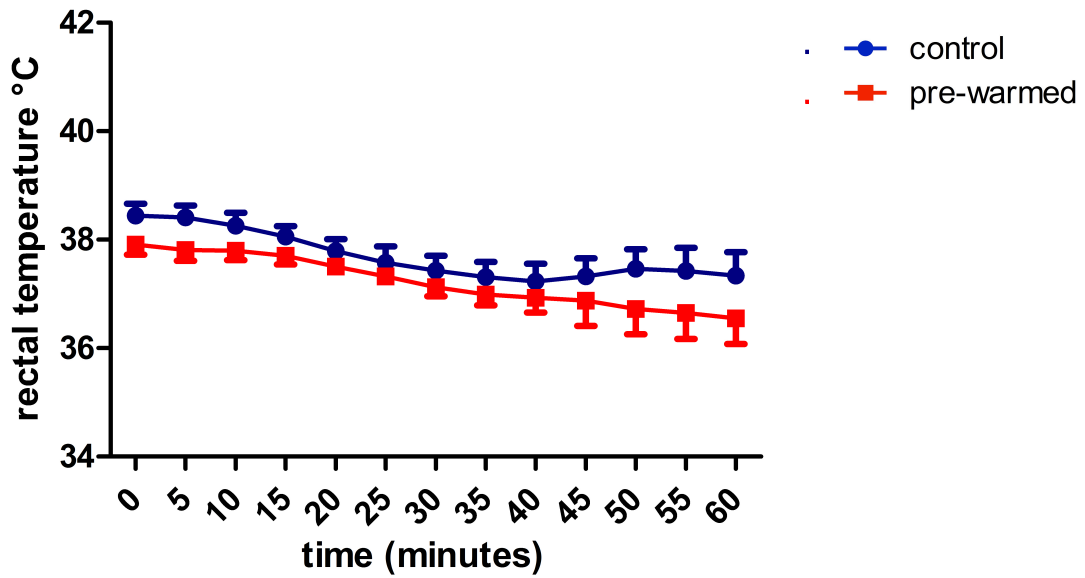
No difference was found in temperature decrease during the first hour of anaesthesia between groups in cats and dogs.

The following graphs show the changes in temperature, recorded every 5 minutes, during the first hour of anaesthesia in the different groups.



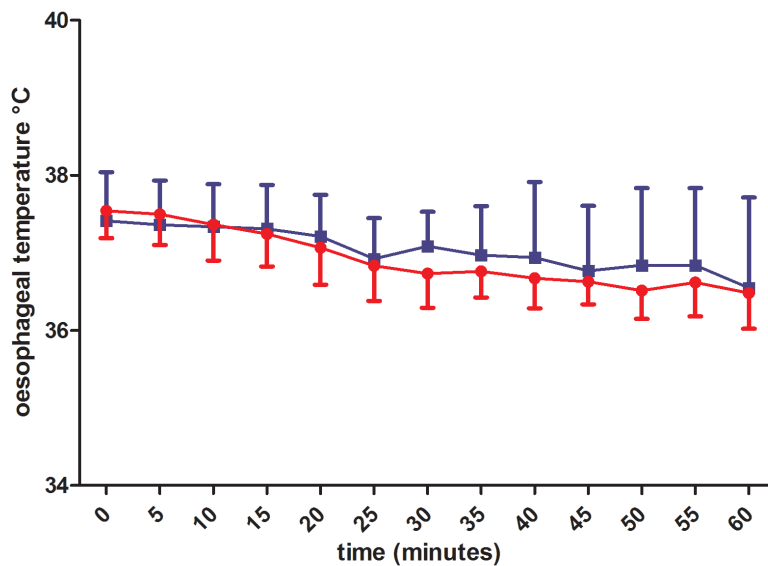
Graph 1. Comparison of oesophageal temperature over time in pre-warmed and control cats.

Rectal Temperature in Cats



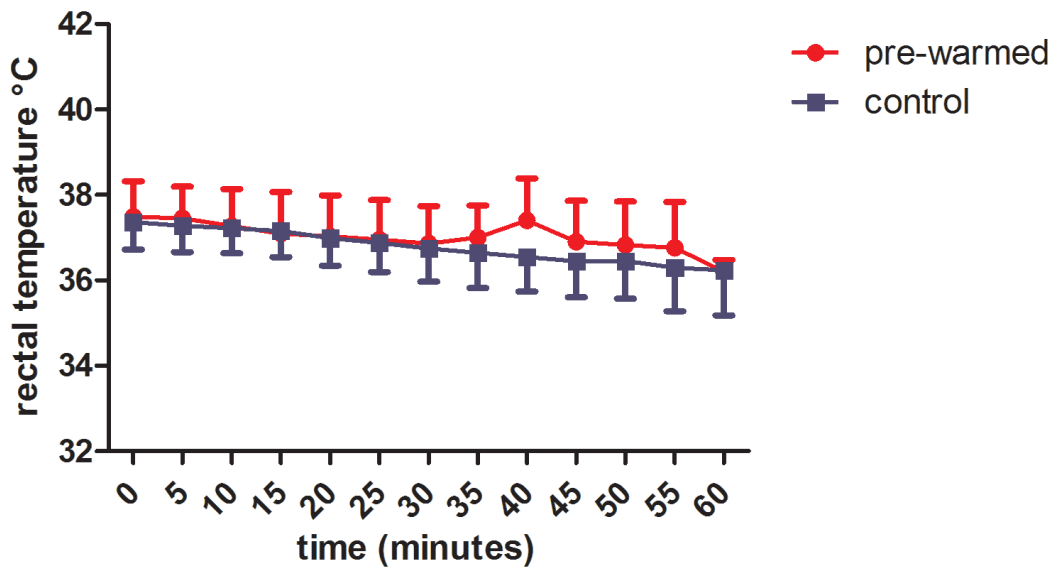
Graph 2. Comparison of rectal temperature over time in pre-warmed and control cats.

Oesophageal Temperature in Dogs



Graph 3. Comparison of oesophageal temperature over time in pre-warmed and control dogs.

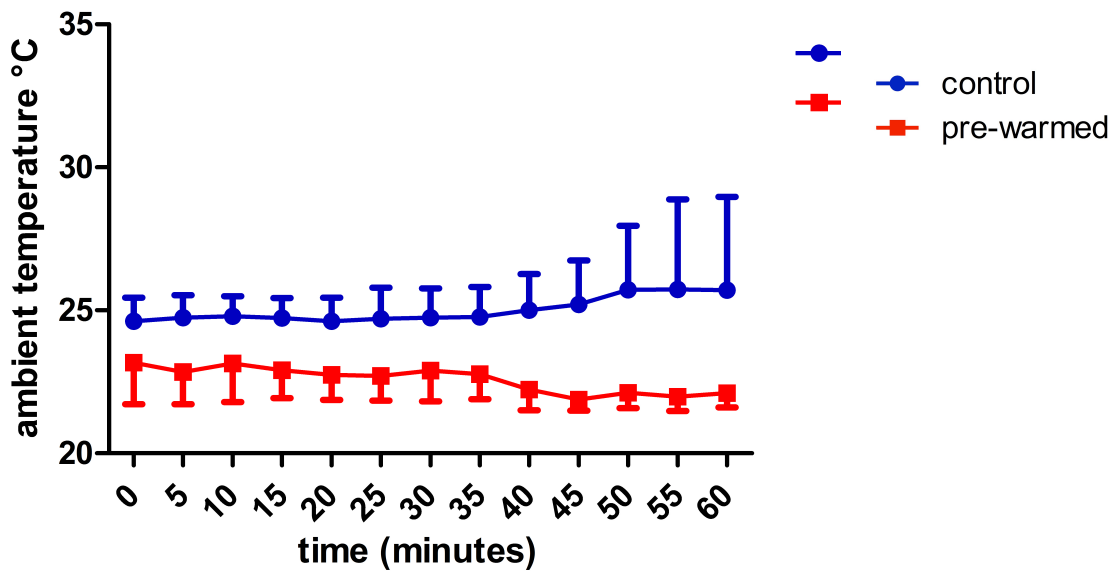
Rectal Temperature in Dogs



Graph 4. Comparison of rectal temperature over time in pre-warmed and control dogs.

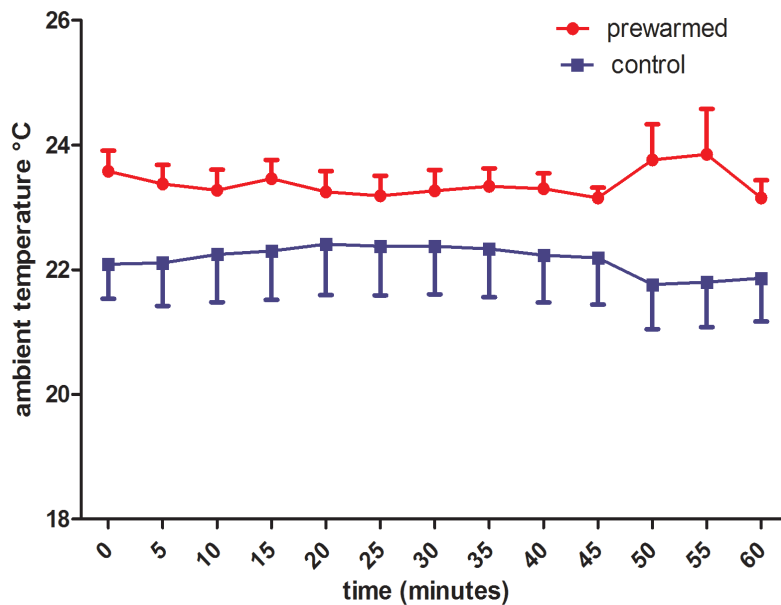
Ambient temperature was lower in controls compared to pre-warmed dogs throughout the study, and higher in controls compared to pre-warmed cats from 5 minutes ($P < 0.05$).

Ambient Temperature for Cats



Graph 5. Comparison of ambient temperature over time in pre-warmed and control cats.

Ambient Temperature for Dogs



Graph 6. Comparison of ambient temperature over time in pre-warmed and control dogs.

6. DISCUSSION AND CONCLUSION

6.1 STUDY DESIGN

Only animals considered healthy or with mild systemic disease not limiting normal function (ASA I and II) were enrolled. This choice was made to avoid possible influence of concurrent pathologies on temperature regulation. It has been shown that certain pathologies (for example hypothyroidism) and critical conditions may predispose the patients to develop hypothermia. (Johnson 2007).

A cut off weight of 10 kg has been chosen as animal of small size are more prone to develop hypothermia, compared to larger breeds, due to high surface area/body weight ratio. Furthermore the dimension of the incubator limits its use to patients of small size.

The anaesthetic protocol was standardized to avoid any influence of drugs and anaesthetic depth on body temperature as much as possible. The same drugs were used for pre-anaesthetic medication, induction and maintenance of all dogs and cats. Oxygen flow of 200 mL/kg/minute was kept constant to minimize the influence of fresh gas flow rate on body temperature. Intravenous fluids rate of 5 mL/kg/hour was standardized for the same reason and fluids were kept at room temperature. Both fresh gases and cold intravenous fluids are known to decrease body temperature in anaesthetized animals. A heat and moisture exchanger (HME) was placed between the endotracheal tube and the breathing system of all animals. The function of these devices is to conserve the heat of the exhaled breath and use it to warm the inhaled gases. They are particularly useful when high fresh gas flow is used in non-rebreathing systems (Hughes 2007). In the awake patient, inspiratory gases are warmed in the nasal cavity and pharynx, and when they reach the second bronchial bifurcation their temperature is similar to body temperature, and absolute humidity is 44 mg/L (McFadden1985). In the anaesthetised patient, when the endotracheal tube is in place, the inspired gases bypass this natural gas conditioning, and they reach the alveoli

relatively dry and cold. This could cause thickening of airway secretions, inflammation and destruction of airway epithelium and hypothermia (Branson 1992). Heat and moisture exchangers are often used to heat and humidify medical gases, as they partially return the exhaled heat and moisture to the next inspiration. These devices are usually made of a transparent plastic housing that allows any secretions in the device to be seen easily. The housing contains a layer of foam or paper coated with a hygroscopic salt (calcium chloride). During expiration, the expired gases cool down passing through this layer, causing condensation. During inspiration, the dry gases are warmed and humidified by the condensate that evaporates using the absorbed heat (Wilkes 2010).

Anaesthetic depth is another important factor influencing temperature regulation in the anaesthetised patient. Deep levels of anaesthesia contribute to on going losses of body temperature by depressing heat production and promoting heat loss. Stoen (1990) demonstrated that isoflurane produces a dose dependent lowering of the threshold for thermoregulatory vasoconstriction. The dose dependent curve is approximately linear up to 1.5 MAC and the thermoregulatory threshold was decreasing by about 3°C% isoflurane concentration. In the present study animals were maintained with isoflurane with the vaporiser set at 2% and adjusted only if necessary. The individual variation in anaesthetic depth typical of every patient, might have influenced the body temperature during the study period.

All the study animals underwent minor surgical procedure. Animals admitted for major soft tissue or orthopaedic surgeries were not enrolled in the study. The reason for excluding more invasive surgeries was to limit the effect of the procedure on body temperature. Abdominal surgery, orthopaedic surgery or any kind of invasive surgery will further decrease the body temperature due to large surgical prepared areas and heat evaporation from the surgical field (Roe 1971). In this study procedures with no or minimal surgical preparation were chosen, and procedures involving opening of any body cavity were excluded. We hope that this minimized the effect of the procedure on the decrease in body temperature during general anaesthesia.

Multiple clinical and experimental studies, both in humans (Whitby 1968, 1971) and in animals (Shanks 1974) have shown oesophageal temperature to be reliable as indicator of mean body heat content; but it has been shown that oesophageal temperature can vary markedly depending on the site in which it is taken. Whitby (1968) reported in humans the lower fourth of the oesophagus to be both the warmest and most reliable. In the present study, the oesophageal temperature probe was inserted till the level of the heart, estimated by holding the probe on the side of the animal before oesophageal placement. Position of the probe was not confirmed radiographically in all cases, hence slight variations in probe position could have affected the temperature measurements.

Rectal temperature at premedication time was measured with a digital rectal thermometer. After induction of anaesthesia temperature rectal and oesophageal temperature was measured with probes connected to multiparameter monitors (Mindray PM 8000 Vet or Dynascope Fukuda Denshi). The use of different temperature probes may have decreased the accuracy of the measurements.

During the study period animals lay on an incontinence pad and no warming devices (with the exception of the HME) were applied. If the oesophageal temperature was decreasing down to 36°C, active warming was started and the study was discontinued for that animal. The temperature of 36°C was considered a level of hypothermia below which it was ethically unacceptable to not to warm the animal actively. If 36°C were reached, active warming was installed by mean of air warmed blankets, heated pads and normal blankets. The 36°C cut off point is a limitation as shortened the study time for several animals, reducing the amount of data available. When general anaesthesia was discontinued, animals with an oesophageal or rectal temperature below 37.5°C were recovered in an incubator with temperature set at 33°C, until normothermia was achieved.

6.2 RESULTS

Three dogs were excluded from the study as they did not tolerate the pre-warming period in the incubator. These dogs were one pug, one West Highland white terrier and a bichon frise. The dogs became stressed and agitated while in the incubator, hence the decision of removal from the incubator and exclusion from the study. Pre-warming in an incubator might not be a suitable method for all small animals as some of them could become excessively stressed and hot in a small cage. This may be particularly important for brachycephalic dogs, in which overheating associated with sedation can quickly exacerbate the brachycephalic obstructive airway syndrome with a high risk of upper airway obstruction. For this reason, all animals, but in particular brachycephalic breeds, must be closely monitored during the pre-warming period to avoid distress due to overheating.

Also in humans it has been shown that a rapid increase in skin temperature leads to thermal discomfort. Such discomfort limits the tolerable duration of aggressive warming (Sessler 1995). When a level of thermal discomfort is reached, sweating in humans, and panting in animals, begins, to decrease body heat content. This will ultimately oppose to the warming efficacy.

Multiple clinical and experimental studies, both in humans (Whitby 1968, 1971) and in animals (Shanks 1974) have shown oesophageal temperature to be reliable as indicator of mean body heat content. Although rectal temperature is most commonly measured, it may not be an accurate reflection of true body temperature, especially in case of rapid temperature changes. During rapid cooling, differences up to 4°C have been detected between oesophageal and rectal temperature (Trede 1961). In a more recent study in cats (Machon 1999), rectal and oesophageal temperatures recorded under anaesthesia did not differ significantly, although mean rectal temperature was slightly higher. In human patients, rectal and oesophageal temperature did not show a close correlation, whereas aural temperature showed a very close correlation with oesophageal temperature (Holdcroft 1978).

In the present study oesophageal and rectal temperature were weakly correlated in dogs and not correlated in cats. The result emphasises the utility

of measuring oesophageal temperature under general anaesthesia rather than only rectal, as the presence of faeces, probe position or vasoconstriction may alter temperature readings. Aural temperature is not a common site of temperature measurement in small animals, due to the length and tortuosity of the external ear canal (Machon 1999).

Rectal temperature was measured just before pre-anaesthetic medication and immediately after induction of anaesthesia. It was not measured before induction as it was considered a possibly stressful procedure with no benefit for the animal.

There was no difference between baseline temperature and temperature taken immediately after induction in dogs and cats, and pre-warming did not help in decreasing the degree of heat loss under general anaesthesia. There could be several explanations for this result.

First of all, the time spent in the incubator or the temperature set might not be appropriate to improve body temperature in small animal patients.

Sessler (1995), tried to identify the optimal temperature and minimum warming duration likely to substantially reduce redistribution hypothermia. Healthy volunteers were warmed for two hours with a Bair Hugger forced-air heater. After 30 minutes warming, peripheral heat content was increased by 69 ± 14 kcal. After one hour extremity heat content had increased by 136 ± 28 kcal. The amount of heat redistributed during the first hour of anaesthesia is about 46 kcal, with an additional core to peripheral transfer of 17 kcal in the sequent two hours (Matsukawa 1995). Redistribution is not the only cause of intraoperative hypothermia, however, under test condition it accounted for 65% of the hypothermia observed after 3 hours of anaesthesia. This could explain why pre-warmed patients may remain normothermic even after 3 hours of major surgery (Just 1993). Thus it is predictable that redistribution hypothermia in surgical patients is markedly reduced by 30 minutes of forced air warming and virtually eliminated if active heating is maintained for an hour (Sessler, 1995).

In our study it was decided to limit the pre-warming time to thirty minutes, as a longer time was considered clinically impractical. This time might have been

too short to reduce redistribution hypothermia, possibly due to the high surface area to body ratio in small patients compared to humans, that predispose to a quicker and more severe loss of heat after induction of general anaesthesia.

The animals in the study were pre-warmed in an incubator set at 33°C, temperature which might have not been adequate, but higher temperatures would most likely not be easily tolerated by animals, especially if only mildly sedated.

Another reason for a failed increase in temperature after the incubator period could be related to the drugs administered as pre-anaesthetic medication. The sedation protocol was a combination of 20 µg/kg buprenorphine intramuscularly and 20 µg/kg of acepromazine. Buprenorphine is a partial µ opioid receptor agonist and, as all opioids, acts on the central thermoregulatory centre. The effect of opioids on the thermoregulatory centre is to reset the temperature at a lower level in dogs. For this reason dogs tend to cool themselves, panting, after opioids administration. This heat dispersion may contribute to the development of hypothermia after pre-anaesthetic medication. Acepromazine causes vasodilation by blocking α_1 receptors. Vasodilation might increase the speed of heat gain while the animal is inside the incubator, but once taken out from it, heat is lost quicker, as it easily flows from the central compartment to the periphery.

What we believe is the most likely cause of the little effect on body temperature of the pre-warming time, and a major study limitation, is the prolonged time that animals spent out of the incubator before induction of anaesthesia. This time was 23 ± 12.5 minutes in dogs and 19.6 ± 7.5 minutes in cats. This time delay was mainly due to intravenous catheter placement and delays of anaesthetic induction due to clinical organization. In this period spent outside the incubator is likely that animals lost the previously gained heat, hence losing the benefit of pre-warming. This cooling down effect might have been particularly enhanced due to the small size of the animals and the effect of sedatives as previously discussed. Unfortunately for ethical reasons it was not possible to measure rectal temperature immediately after the thirty minutes spent in the incubator, as of no benefit for the animals, so there is no

possibility to know if the incubator was not effective or if the heat was lost in the delayed time.

Several human studies showed how pre-warming was efficacious in reducing hypothermia during general or regional anaesthesia, but failed in demonstrating an increase in core temperature after the pre-warming period (Melling 2001, Hynson 1993). Pre-warming has been shown to increase skin temperature, but not core temperature, thus reducing the temperature gradient between core and peripheral compartments and the heat flux between them. This could also explain why, in the present study, there was no difference in core temperature between pre and post warming period. Furthermore, the aim of pre-warming is not an increase in base line body temperature, but is mainly a decrease in heat loss during general anaesthesia.

Another possible factor affecting the results of this study is ambient temperature. Room temperature is an important factor in determining heat balance in the anaesthetised patient as heat flow is dependent on thermal gradient between patient and environment. An increase in room temperature will decrease the thermal gradient, thus minimizing heat loss (Bissonnette 1991, Morris 1971). In human adults ambient temperature below 22°C will cause hypothermia under general anaesthesia (Morris 1971), whereas infants and neonates require temperatures as high as 26°C at least (Bissonnette 1991). This is relevant as operating room staff is more comfortable in a cooler environment, whereas the maintenance of the patient body temperature may require a warm environment.

In animals the ideal ambient temperature to maintain normothermia under anaesthesia has not been described. However dogs anaesthetised became hypothermic when ambient temperature was below 27°C (Dale 1968). In the present study ambient temperature was lower in controls compared to pre-warmed dogs (23.7 ± 1.3 versus 21.6 ± 1.5 respectively) throughout the study, and higher in controls compared to pre-warmed cats (23.5 ± 1.4 versus 23.9 ± 1.7 respectively) from 5 minutes ($P < 0.05$). Even if the ambient temperatures were statistically different, they would still have provided a significant gradient

of heat loss from the animals to the environment, possibly minimally affecting the amount of heat loss.

Tunsmeyer (2009) demonstrated that dogs under 10 kg warmed with heated pads and covered with a reflective blanket maintained a higher temperature intraoperatively compared to dogs warmed only with heated pads.

This suggests that the use of multiple heating methods simultaneously provides the best results on body temperature. Kibanda (2012) also showed how forced air warmed blankets and heated mat devices were not sufficient, on their own, to maintain normothermia in dogs undergoing general anaesthesia. This would indicate that several methods of rewarming, rather than one, should be adopted during anaesthesia. This was also confirmed by a previous study (Tan 2004) in which dogs warmed perioperatively with both a heated mat and a radiant heat lamp were significantly warmer than dogs being warmed by one heating device only. Rembert (2004) demonstrated how a forced air warmer was much more effective when accompanied by a simple plastic drape, in increasing the microenvironment temperature.

One of the largest randomized trial of pre-warming in humans was that by Melling (2001) involving 421 patients. Patients in the pre-warming group received 30 minutes of either systemic or local warming. The study was powered to look for differences in postoperative complications and showed a significant decrease in postoperative wound infections in patients who were pre-warmed. However there was no difference in incidence in perioperative hypothermia between the groups. The author suggested that pre-warming improved peripheral circulation in the perioperative period, thus increasing tissue oxygenation. This suggests that even if pre-warming may not have a positive effect in reducing hypothermia, it has other advantageous effects perioperatively.

In conclusion, pre-warming for thirty minutes in an incubator was not an adequate method to reduce hypothermia in small animals under general anaesthesia. To avoid possible loss in temperature after pre-warming, the time between pre-warming period and induction of anaesthesia should be

minimized and animals should be insulated with blankets or bubble wraps once outside the incubator.

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