Evaluation of core temperature measurement and treatment of capture-related hyperthermia in anesthetized brown bears (*Ursus arctos*)

by

Larissa Mourad Ozeki

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Abstract

The objectives of the present study were to: 1) compare body temperature of anesthetized brown bears obtained by Vital Sense® capsules (VS) inserted gastrically to those obtained by deep rectal VS and handheld digital thermometer (HDT) and 2) to evaluate the decrease in core body temperature produced by an active cooling protocol and by alpha-2 antagonism. Thirty-one brown bears were captured with a combination of zolazepam-tiletamine and xylazine or medetomidine. One VS capsule was inserted deep into the animals’ rectum and another into the stomach. Rectal temperature was also measured with the HDT and paired data points were analyzed with the Bland-Altman technique and regression analysis. In bears that demonstrated gastric temperatures $\geq 40^\circ$C a described active cooling protocol was performed and the temperature change was analyzed for 30 minutes. To determine if antagonism of the alpha-2 agonist decreased core body temperature in bears, change in temperature was analyzed for 30 minutes after the administration of IM atipamezole. A third group of bears were not cooled and temperatures were recorded for 30 minutes before administration of atipamezole. To compare the differences among the three groups an area under the curve was calculated for each individual bear and analyzed one-way analysis of variance with Tukey’s PostHoc test. To evaluate the change over time within each treatment a General Linear Model for repeated measures was performed, with Tukey’s PostHoc test. The significance level of all analyses was 5%. VS capsules accurately measured core temperature and HDT did not accurately estimate core temperature in anesthetized brown bears. The active cooling protocol used significantly decreased body temperature of hyperthermic bears after 10 minutes. Alpha-2 antagonist produced an earlier significant decrease but the final change in temperature (at Time 30) was lower than with active cooling. No significant difference was found between the two treatments.
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To my niece, Manuela.
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<td>Atp</td>
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<td>AUC</td>
<td>Area under the curve</td>
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<td>DRVS</td>
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<td>Respiratory rate</td>
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“I learned that courage was not the absence of fear, but the triumph over it. The brave man is not he who does not feel afraid, but he who conquers that fear.”

Nelson Mandela
CHAPTER 1: INTRODUCTION AND LITERATURE REVIEW

1.1 Introduction

Many wildlife species develop hyperthermia during capture due to high ambient temperatures, physical exertion, stress and use of drugs that impair thermoregulation (Sillero-Zubiri 1996; Citino et al. 2001; Meyer et al. 2008; Fahlman et al. 2011) and it can be a life threatening complication (Simon 1993; Bouchama & Knochel 2002). However, in the current literature there are only few studies that evaluate currently used methods for treating capture-related hyperthermia in wild animals (Sawicka 2010).

1.1.1 Literature Review

1.1.1.1 Pathogenesis and pathophysiology of capture-related hyperthermia

Immobilation is the first step in many research studies and health care procedures of free-ranging and captive wild animals. Currently the reliability of a capture protocol is not only measured by risk to staff safety, but also by animal welfare (Arnemo et al. 2006). Many wild species can develop hyperthermia (body temperature ≥ 40.0 °C) during capture due to several factors: high ambient temperature (Cattet et al. 1997; Sawicka 2010), stress (Kreeger et al. 1990; Meyer et al. 2008), intense physical activity (Fahlman et al. 2008) and use of drugs that impair thermoregulation (Cattet et al. 2003a; Cattet et al. 2003b). Hyperthermia is a life threatening complication and its consequences will be better discussed further in this chapter.

In reviewed cases of capture-related hyperthermia reported in the current literature, it is noticeable that multiple risk factors may play a role, alone or in combination, in increasing body temperature during capture and handling. Roan antelopes (*Hippotragus equinus*) anesthetized with a combination of thiafentanil, medetomidine and ketamine had body temperature ranging from 38.0 °C up to 40.3 °C (mean of 39.5°C ± 0.6°C) (Citino et al. 2001). The roan antelopes
were herded into a boma with a helicopter and darted after calming down for several hours (Citino et al. 2001). Hyperthermia was observed even though the procedures were performed when ambient temperatures were low (Citino et al. 2001). In another study, wolverines (Gulo gulo) captured by different methods including helicopter darting, ground darting and snare poles, showed very high indices of hyperthermia (91.6 %) among the adult subjects (Fahlman et al. 2008).

Stress had the greatest impact on the occurrence of hyperthermia in impala (Aepycerus melampus) (Meyer et al. 2008). The impala that were pursued but not captured had higher body temperatures than the animals that were immobilized after short pursuit times (Meyer et al. 2008). Likewise, the impala that were habituated to human presence had lower body temperatures and plasmatic cortisol levels, when compared to naïve subjects (Meyer et al. 2008). Three of the naïve impala died after developing body temperatures greater than 43.0 °C in one of the two anesthetic procedures (Meyer et al. 2008). Another important finding is the fact that the impala that were not captured, but were watching a group member being captured, developed hyperthermia as well, indicating potential physiological damage to non-subject animals (Meyer et al. 2008).

Captive polar bears (Ursus maritimus) had lower body temperatures than free-ranging polar bears anesthetized with the same drug combination (Cattet et al. 2003b). A high occurrence of hyperthermia was also observed in free-ranging brown bears (Ursus arctos), in contrast to captive brown bears, which did not present hyperthermia (Fahlman et al. 2011). It is important to emphasize that free-ranging bears from the aforementioned studies were captured by helicopter darting after pursuit (Cattet et al. 2003b; Fahlman et al. 2011). Captive bears did not experience
pursuit before anesthesia and this might be the reason why a greater occurrence of hyperthermia in free-ranging bears was observed (Cattet et al. 2003b; Fahlman et al. 2011). As previously mentioned, of 91.6% of the all captured adult free-ranging wolverines had temperatures greater than 40 °C. However, no correlation was found between the occurrence of hyperthermia and the different capture methods: helicopter darting, ground darting and the use of snare poles (Fahlman et al. 2008).

Physical exertion and high ambient temperature exposure can lead to heat stroke in humans, which is a form of hyperthermia that is associated with a generalized inflammatory process (Bouchama & Knochel 2002). This inflammatory process generates a syndrome causing multiple organ dysfunction in which encephalopathy prevails (Bouchama & Knochel 2002). The normal thermoregulation pathway consists of: detection of a cold or warm stimulus by the A-delta or C fibers (respectively); projection of stimuli to the central nervous system; regulation in the preoptic-anterior hypothalamic area (POA); and efferent responses according to the type of stimulus (Kurz 2008; Sessler 2009).

A hyperthermic state is developed when there is an imbalance between metabolic heat production and body heat loss (Bouchama & Knochel 2002; Sessler 2009). In humans, approximately 90% of the heat loss occurs through the surface of the skin (Kurz 2008). There are four mechanisms for heat loss: convection, radiation, evaporation and conduction (Wheeler 2006). Convection accounts for 30% of body heat loss in humans and is the exchange of heat with the air around the subject, which increases with air movement (Wheeler 2006). Radiation is the exchange of heat with an object close but not in direct contact with the body, and accounts for 40% of heat loss on the anesthetized human patient (Wheeler 2006). Heat loss via
Evaporation occurs when energy is used to transform the moisture on the surface of the subject into a gas; it represents 25% to 30% of body heat loss in humans (Wheeler 2006). Finally, conduction is the heat exchanged with an object in direct contact to the body and it is not considered an efficient mechanism to lose heat in human subjects (Wheeler 2006).

Sympathetic vasodilation produces an increase in the blood flow within the skin of up to 8 liters per minute in humans; this increases the delivery of heated blood to the periphery of the body (Bouchama & Knochel 2002; Wheeler 2006). The peripheral blood flow then allows heat to dissipate to the environment mostly through convection and radiation (Wheeler 2006). Evaporation through the production of sweat in humans depends on the water saturation of the air surrounding the skin (Bouchama & Knochel 2002). In animals such as the brown bear, where skin sweat glands are very limited in distribution, salivary secretion and panting may also contribute to heat loss via evaporation (Morrison & Nakamura 2011). Behavioral responses animals use to minimize heat gain include reduction of muscular activity and moving to the shade, but these responses do not occur in anesthetized patients (Wheeler 2006).

Deviations from normal body temperature affect the molecular properties of cells, such as enzyme efficiency, diffusion capacity and membrane fluidity (Repasky & Issels 2002). These alterations can harm cellular normal function and cause cell degeneration, cell death and related tissue injury within many body systems (Bouchama & Knochel 2002; Morrison & Nakamura 2011). Thus, hyperthermic damage at a cellular level may increase capture related morbidity and mortality. Hyperthermia increases oxygen consumption and the resulting hypoxemia can induce convulsions, brain hypoxia and death (Simon 1993). Human patients with heat stroke are more susceptible to infections and may develop disseminated intravascular coagulation (Bouchama &
Elevated body temperatures can also impair reproductive function in mammals, since it affects gamete formation and function, embryo development and fetal growth (Hansen 2009). These physiological impacts can be detrimental for conservation of wild species.

Arnemo et al. (2006) reported mortality rates during anesthesia of several species of free-ranging wildlife over two decades in Scandinavia and concluded that only 0.1% of the animals died due to direct effects of the anesthetic drugs used in the species studied – hyperthermia was considered as one of these direct effects. However, the mortality rates related only to hyperthermia were not reported, nor were morbidity rates easy to measure. Death of one anesthetized polar bear in another study was related to hyperthermia (Cattet et al. 2003b). The polar bear developed a high rectal temperature (42.6°C) during anesthesia and, despite treatment with cold water enemas and intravenous atipamezole, the bear died following multiple convulsive episodes. Two black bears were also reported to have died, the deaths were possibly due to hyperthermia when immobilized with ketamine and xylazine after snare capture (Hellgren & Vaughan 1989).

1.1.1.2 The anesthetic drugs’ influence on capture-related hyperthermia in bears

For more than two decades from the late 1970’s into the 1990’s, the drug protocol of choice for most species of bears was a combination of zolazepam hydrochloride and tiletamine hydrochloride (Stirling et al. 1989; Gibeau & Paquet 1991; White et al. 1996). When using zolazepam-tiletamine alone, Bush et al. (1980) reported that one supplemental dose of the anesthetic association was needed in one-third of the cases, and that a second top-up dose was required in more than half of the bears that received a first supplemental dose. The authors considered that the recovery time was prolonged due to repeated drug administrations. When
zolazepam-tiletamine is combined with alpha-2 adrenergic agonists such as medetomidine or xylazine, several advantages can be observed: less need for top-up doses, reversibility of the alpha-2 agonist and shorter recovery time (Cattet et al. 1997; Cattet et al. 2003; Cattet et al. 2003a). The addition of an alpha-2 agonist also allowed a reduction of the required dose of zolazepam-tiletamine in grizzly bears and a reduction of the final drug volume by up to 45 % (Cattet et al. 2003a). By reducing the volume of administration, low impact distance injection systems may be used, this decreases the risk of injuries caused by high impact dart systems required when volumes are high (Cattet et al. 2003a). Currently combinations of an alpha-2 adrenergic agonist and zolazepam-tiletamine are considered the most reliable protocol for chemical immobilization in bears; therefore this section will focus on the alpha-2 adrenergic agonists’ mechanism of thermoregulation impairment.

Alpha-2 adrenergic agonists are sedative drugs that modulate the release of norepinephrine from central and peripheral neurons, acting on the post synaptic alpha-2 adrenoceptors causing a decrease in sympathetic flow. This promotes sedation, analgesia, bradycardia, vasoconstriction, as well as a decrease in respiratory rate and salivation in some species (Jalanka & Roeken 1990; Maze & Tranquilli 1991). Xylazine has been used since the 1980’s in different species of wild and domestic animals (Bush et al. 1976; Addison & Kolenosky 1979; Lee et al. 1981; Mech et al. 1985; Renecker & Olsen 1986; Kokkonen & Eriksson 1987). Medetomidine is a more recent developed alpha-2 agonist that is ten times more potent, selective and specific for alpha-2 adrenoceptors than xylazine (Virtanen et al. 1988).

In spite of several advantages, the alpha-2 agonists may impair thermoregulation and, consequently, cause or worsen hyperthermia (Bill et al. 1989; Feleder et al. 2004) and
hypothermia (Quan et al. 1992; Livingston et al. 2012). Vasoconstriction plays an important role preventing body heat from dissipating to the environment (Sessler 2009; Morrison & Nakamura 2011). When pursued, stressed or struggling, wild animals increase their body heat production (Kruk et al. 1985) and alpha-2 induced vasoconstriction may impede the loss of this excessive metabolic heat to the environment. The behavioral responses of wild animals to capture events and the physiologic effects of alpha 2 agonists may act synergistically to increase the likelihood of hypothermia during capture events.

The central mechanism of the alpha-2 adrenergic agonist induced hyperthermia remains unknown. A high positive correlation was found between the activation of alpha-2 adrenoceptors, following injection of clonidine into the pre-optical hypothalamic area of conscious guinea pigs, and a concurrent increase in prostaglandin E$_2$ (PGE$_2$) concentrations, which promoted thermogenesis via the inflammatory process (Feleder et al. 2004). Hyperthermia is induced by elevation of PGE$_2$ in the brain (Oka 2004). The inflammatory stimuli that PGE$_2$ induces can cause hyperthermia either by cyclooxygenase-2 and microsomal synthase of PGE in the endothelial cerebral cells (Oka 2004). Clonidine also acts on imidazoline receptors (Khan et al. 1999), which makes it difficult to attribute its effect to alpha-2 adrenoceptor action alone. When administered after the alpha-2 adrenergic antagonist yohimbine, clonidine failed to produce thermogenesis in guinea-pigs, which could be further evidence that the central thermogenic properties of clonidine are attributed to its action on alpha-2 adrenoceptors (Feleder et al. 2004). However, yohimbine can also act on alpha-1 adrenergic receptors; therefore it is difficult to conclude that the release of prostaglandin E2 was caused solely by central stimulation of alpha-2 adrenoceptors.
The third manner in which alpha-2 agonist can influence thermoregulation is related to behavioral responses to promote heat loss, such as postural changes, movement to a colder environment and release of saliva (Morrison & Nakamura 2011). These reactions are abolished during anesthesia and as they are known to be the most effective thermoregulatory responses in humans, this effect may be severe (Kurz 2008). The lack of behavioral responses summed with concurrent vasoconstriction and central thermogenesis leads to the persistence of hyperthermia, since all effects contribute to decrease in heat loss.

When comparing the effects of the use of zolazepam-tiletamine and zolazepam-tiletamine combined with xylazine, the alpha-2 combination significantly increased body temperature and thus, the risk of hyperthermia, in grizzly bears (Cattet et al. 2003a). However, in polar bears, no statistical difference was observed in the mean body temperature when comparing animals anesthetized with xylazine combined with zolazepam-tiletamine, to those anesthetized only with zolazepam-tiletamine (Cattet et al. 2003b). Despite no statistical difference in the mean body temperature between the two groups, temperature of the polar bears anesthetized with the alpha-2 agonist combination increased significantly over time, in contrast to those anesthetized with only zolazepam-tiletamine, in which body temperatures decreased over time. In this study, the polar bears were capture during hypo-metabolic season. Thus, their body temperatures when anesthetized were lower than what would be observed in bears during the active season.

1.1.1.3 Common and novel methods of monitoring temperature in the field

A common method of monitoring body temperature during wildlife capture is the use of handheld thermometers to measure rectal temperature (Hellgren & Vaughan 1989; Fernandez-Moran et al. 2001; DelGiudice et al. 2005; Fahlman et al. 2008; Fahlman et al. 2011). However,
there is evidence that this is not an accurate method to estimate core temperature (Iaizzo et al. 1996; Cattet et al. 1997; Robinson et al. 1998). In reported cases of hyperthermia encountered during field capture, a common procedure used for treatment is the rectal administration of cold water enemas (Cattet et al. 1997; Deem & Karesh 2001; Foster 2005). When this technique is used, rectal temperature readings could be compromised by the cold water flush and might not provide accurate data on the effects of the treatment.

Auricular (or tympanic) infrared thermometers have also been tested in several species with different outcomes. In dogs, good agreement was found between readings from auricular thermometers measuring tympanic temperatures and glass-mercury rectal thermometers inserted for three minutes into the dogs’ rectum (Sousa et al. 2011). However, when compared to an insertion until the stabilization of the mercury column or to the readings obtained from a digital rectal thermometer, the correlation with the auricular thermometer was found to be unsatisfactory (Sousa et al. 2011). In squirrel monkeys, the human tympanic thermometer was compared with a veterinary tympanic thermometer and a handheld digital rectal thermometer (Long et al. 2011). No statistical difference was found between the human tympanic thermometer and the rectal thermometer; the veterinary tympanic thermometer, in its turn, demonstrated significantly lower reading than the rectal thermometer (Long et al. 2011). Similar results were found in hyperthermic big horn sheep and in normothermic fallow deer, where the tympanic thermometer had significantly lower mean temperature when compared to the rectal thermometer (Drew 1996). In orangutans, tympanic temperature had significant correlation to rectal temperature but the technique was challenging in young subjects (Fahlman et al. 2006). However, the statistical analysis chosen for those studies was not the recommended analysis for methods comparison (Bland & Altman 2007).
Thermistor insertion into the rectum of wild animals is another option for body temperature monitoring in the field (Cattet et al. 1997; Citino et al. 2001; Citino et al. 2002; Radandt 2009). Possible limitations include the requirement to carry and use an additional piece of sensitive field equipment and the possibility that extreme ambient temperatures might influence the readings obtained, since part of the device stays exposed during the monitoring. To date this fact remains unknown.

The VitalSense® (VS) is a telemetric monitor consisting of a data receiver and logger which records every 15 seconds data from a temperature sensor, which can be either a core body temperature capsule (designed to be swallowed by the human patient), or a dermal patch (designed to measure skin temperature). The advantages of the VS monitor is that the monitor recognizes each capsule by a unique identification number (McKenzie & Osgood 2004) and can therefore record information from more than one sensor at a time. This differs from other indigestible temperature systems which will only record information from a single sensor. Moreover, the monitor reads data only from capsules that were activated on that specific monitor, which provides no interference between two capsules or subjects proximity. In the present study, it allowed comparison between two different insertion methods of the capsules in the same animal, recorded by the same VS monitor. The VS data is downloaded in form of a spreadsheet as show in Appendix A.

The VS core temperature capsules are 23 mm in length by 8.7 mm in diameter, weigh 1.6 g, have range of transmission of 1 m, accuracy to within ± 0.10 °C in body temperature range of 32 °C to 42 °C and resolution of 0.01 (Darwent et al. 2011). In humans core body temperature capsules swallowed by the subjects were compared to rectal probes inserted 11 mm deep into the rectum, which are considered to be the “gold standard” for core temperature monitoring.
(McKenzie & Osgood 2004). The mean difference between the two methods (rectal temperature minus core body temperature capsule temperature) was 0.04 °C ± 0.03 °C, which was considered to be a good agreement. In animals, gastric placement of the core temperature capsules demands time, special skills and a light plane of anesthesia, to avoid swallowing and vomiting (Guedel 1927). During wildlife capture a veterinarian is often not present and the anesthetic time must be kept to a minimum. These factors will increase the challenge of gastric placement, and may limit the application of this technique in the field.

There are other types of telemetric thermometry devices such as temperature loggers. However, these loggers are designed to be surgically implanted into the animals’ abdominal cavity and they do not provide real time and continuous readings, since they need to be surgically removed to have the data recorded extracted by a receiver (Meyer et al. 2008; Torrao et al. 2011). There are different temperature loggers that can be inserted subcutaneously, however their accuracy estimating the core temperature was not considered satisfactory in goats since its readings were up to 4 °C lower than core temperature (Torrao et al. 2011).

1.1.1.4 Treatment of hyperthermia

When capture free-ranging wild animals, equipment and supplies that can be carried to the field are limited. Cooling therapies that can be used in the field include: placing the animal in the shade, fanning, external cooling with water and/or snow, administration of intravenous fluids, intranasal oxygen supplementation and administration of cold water enemas (Cattet et al. 1997; Fahlman et al. 2008; Arnemo et al. 2011; Fahlman et al. 2011). The effect of cooling protocols on true core temperature in hyperthermic bears is unknown. When using cold water enemas, once cold water is administered into the rectum, traditional measurement of rectal temperature will most likely underestimate core body temperature.
The gold standard technique for cooling in human cases of exertional hyperthermia is cold water immersion (Casa et al. 2007). However, this technique is not feasible for free-ranging large mammal captures, unless there is a natural source of cold water close to the capture site. Furthermore, some authors advocate that active cooling techniques produce peripheral vasoconstriction, which would compromise its effectiveness (Wyndham et al. 1959; Kurz et al. 1995; Lenhardt et al. 1999).

In anesthetized normothermic human patients active cooling with forced cold air took longer to produce the same decrement in core temperatures in patients with vasoconstriction than in those who had vasodilation (Kurz et al. 1995). The authors discussed that vasoconstriction can be triggered by low core temperatures (around 34.5°C), but it can also be induced by the use of alpha-2 adrenergic agonist drugs (Kurz et al. 1995). In alert human subjects, external cooling with circulating cold water and air (at 15°C) did not significantly decrease core temperature after interleukine-2 induced hyperthermia. The treatment also provoked extreme discomfort and significantly increased their stress hormones measured in the plasma (epinephrine and norepinephrine) (Lenhardt et al. 1999). The authors argued that external cooling induced vasoconstriction and shivering, which prevented heat dissipation from the skin surface. Furthermore, external cooling also increased the metabolic rate, augmenting body heat production (Lenhardt et al. 1999).

In hyperthermic anesthetized dogs, continuous iced gastric lavage effectively reduced PA temperature (Syverud et al. 1985). This treatment was compared with passive cooling at room temperature and had a cooling rate six times higher. However, the lavage was applied continuously until PA temperature was lower than 38°C. The authors did not report any adverse
effects of the gastric lavage and did not find evidence of post-mortem gastric lesions after necropsies (Syverud et al. 1985).

Yohimbine, rauwolscine and idazoxan effectively prevented clonidine induced hyperthermia in rats, when administered 30 minutes before the alpha-2 agonist (Mogilnicka et al. 1985). The effectiveness of idazoxan, a selective alpha-2 antagonist, at preventing the clonidine induced hyperthermia suggests that hyperthermia was induced by the alpha-2 adrenoceptors activation (Mogilnicka et al. 1985). This data also suggests that reversal of alpha-2 agonists may effectively treat capture induced-hyperthermia in bears.

Ketanserin, an antagonist of 5-HT₂ serotoninergic receptors, was considered to be effective at treating and preventing stress induced hyperthermia in elk (Stanley et al. 1986). This drug is used in humans to prevent hypertension during pregnancy and in horses to stimulate granulation tissue growth (Hanff et al. 2005; Podymow & August 2008; Ribeiro et al. 2009; Aljuffali et al. 2011). It causes vasodilation by blocking not only 5-HT₂ serotoninergic receptors, but also alpha-1 adrenergic receptors (Van Nueten et al. 1981; Ramage 1985). The results observed in hyperthermic elk treated with ketanserin indicate that the contribution of vasoconstriction in the development of drug-induced hyperthermia is clinically significant (Stanley et al. 1986). Unfortunately, this drug is only available for veterinary use in Canada as a gel for horses, which would limit its effective use in the field (Health Canada 2012).

1.1.2 Significance

The VS is a telemetric device developed to monitor core temperature via capsule, typically ingested by human patients. In animals, gastric placement of the capsules can be more challenging since it requires more time and skills for gastric intubation. Evaluating the accuracy
of a reading from a temperature capsule placed deep into the rectum of animals in comparison to a core temperature enables the development of a novel and reliable monitoring technique that can be performed by a wider spectrum of professionals working in wildlife capture. Furthermore, evaluation of core temperature, during and after commonly used treatments for hyperthermia, contributes towards a better understanding of these treatment methods and their limitations in free-ranging brown bears. Improved monitoring and treatment of hyperthermia in bears might contribute to a decrease in hyperthermia-related mortality and morbidity in other species of wild mammals.

1.1.3 Aims

The general objectives of the present thesis are to answer the following questions:

I. Do VitalSense® capsules inserted deep rectally accurately measure core temperature in anesthetized brown bears (Ursus arctos)?

II. When compared to both deep rectally and gastrically inserted VitalSense® capsules, do handheld digital thermometers accurately measure core temperature in anesthetized brown bears?

III. Does an active cooling protocol decrease core temperature as measured by gastrically placed VitalSense® capsules in hyperthermic anesthetized brown bears?

IV. Does alpha-2 adrenergic receptor antagonism decrease core temperature as measured by deep rectally placed VitalSense® capsules in brown bears recovering from anesthesia?

A pilot study and two major studies were performed between May 2011 and March 2013. The pilot study was performed in pigs prior to the main studies. These studies were made
possible with the collaboration of the Foothills Research Institute Grizzly Bear Program (FGBP) and the Scandinavian Brown Bear Project (SBBP). To the best of my knowledge, rectal placement of indigestible core body temperature capsules or treatment of capture-related hyperthermia have not yet been evaluated in brown bears. I hope to provide more knowledge to improve the quality of brown bear captures and their population health. I also expect to provide data for further research regarding temperature monitoring and treatment of capture-related hyperthermia in other species of wild mammals.
CHAPTER 2: VALIDATION OF DEEP RECTAL INSERTION OF VITALSENSE® FOR MONITORING CORE TEMPERATURE IN PIGS: A PILOT STUDY

2.1 Background and Objectives

Variations in body temperature can harm cellular function, produce tissue injuries and ultimately cause death (Simon 1993; Bouchama & Knochel 2002). In anesthetized dogs and monkeys, hyperthermia by immersion in hot water was utilized to induce cardiac arrest in all subjects (Eshel et al. 1990). The authors evaluated the subjects in post-mortem exam and concluded that the probable causes were peripheral vascular failure and hypovolemia (Eshel et al. 1990). In a retrospective study, 47% of cats evaluated developed postanesthetic hyperthermia (Niedfeldt & Robertson 2006). However, no mortality or morbidity associated with hyperthermia was reported (Niedfeldt & Robertson 2006). The data suggests that the postanesthetic hyperthermia in cats was a dose-related phenomenon following administration of hydromorphone (Niedfeldt & Robertson 2006).

Hence, body temperature is a vital parameter that should be monitored during anesthesia of animals. The temperature of the core, in a normal situation, tends to be unaffected by heat exchanges with the environment, which happens at the periphery of the body; thus, shell temperature varies in order to maintain the core temperature (Imrie & Hall 1990). During anesthesia, thermoregulatory mechanisms can be affected and an ideal method of monitoring body temperature should accurately estimate core temperature, since there is always a normal variation in shell temperature. When performing anesthesia in a hospital or an experimental facility it is possible to provide accurate monitoring of core temperature by using invasive equipment such as a pulmonary artery (PA) catheter, which is considered a true “gold standard”
for core temperature measurement (Shellock & Rubin 1982). When performing anesthetic procedures in the field, the use of invasive monitoring equipment becomes more challenging.

The objective of this pilot study was to validate, in a controlled setting, a novel technique to measure core temperature that would be accurate, frequent, feasible for field situation, applicable to different mammalian species and easy to perform by a large spectrum of professionals working with wildlife. Temperature readings of deep rectally inserted indigestible core temperature capsules were compared to those provided by thermistor tipped PA catheters, in anesthetized pigs. The study was developed as a pilot study and was performed prior to the field trials with free-ranging brown bears.

2.2 Materials and Methods

The pilot study was approved by the Animal Care Committee of the University of Calgary (Protocol SHC11R-04). Seven male Landrace White pigs were originally anesthetized for a study that continuously evaluated their cardiac output during anesthesia. This pilot study was opportunistically performed in six of these pigs in the experimental facilities of the Faculty of Veterinary Medicine of the University of Calgary during the months of July and August of 2011. The pigs were approximately 12 weeks old and their average body weight was 34 kg (29 kg to 42 kg). The pigs were pre-medicated intramuscularly (IM) with 2.5 µg/kg of hydromorphone (Hydromorphone HP 10 mg/ml, Sandoz Canada Inc., Boucherville, QC, Canada, J4B 7KB), 0.2 mg/kg of midazolam (Midazolam 5mg/ml, Sandoz Canada Inc., Boucherville, QC J4B 7KB) and 1 mg/kg of alfaxalone (Alfaxan 10 mg/ml, Jurox Pty Ltd, Rutherford, NSW, Australia 2320). Following sedation, a dose of approximately 1 mg/kg of alfaxalone was administrated intravenously (IV) until endotracheal intubation was possible. Anesthesia was
maintained initially with isoflurane in 100% oxygen, followed by total intravenous anesthesia with infusion of alfaxalone, lidocaine and midazolam. As part of the study protocol, pigs were instrumented with a thermodilution catheter (OptiQ™ 52511 CCO/ S\textsubscript{v}O\textsubscript{2} catheter, non-heparin, ICU Medical Inc., San Clemente, CA 92673). The catheter has a thermistor on its tip that allows continuous measurement of the PA temperature. One VitalSense\textsuperscript{®} (VS) core temperature capsule (Capsule Sensor, Mini Mitter Company, Inc., a Respironics, Inc. Company, Murrysville, PA 15668) was inserted into the pigs’ rectum to collect paired data and compare the readings of the novel technique to those delivered by the “gold standard”. The capsules were inserted with a 15 cm standard applicator and the VitalSense\textsuperscript{®} monitor (VitalSense Monitor, Mini Mitter Company, Inc., a Respironics, Inc. Company, Murrysville, PA 15668) was placed on the surgical table, close to the animals’ pelvis, until the end of the anesthetic procedure. The VS monitor recorded temperature data from the capsule every 15 minutes following activation. Two of these animals were warmed with convective warming.

The data was analyzed using Bland-Altman technique, to obtain agreement between the two methods. The technique was adapted for repeated measurements, as described by Bland and Altman (2007). The correction consists of incorporating the variance of the differences of each data pair for the same subject and the variance for differences between the averages of the two methods across the subjects on the calculation of the standard deviation of the difference (Bland & Altman 2007). A one-way analysis of variance (ANOVA) was used to determine these variances, where the within subjects’ mean square is the estimated variance within subjects; and the difference between the within subjects’ mean square and the between subjects’ mean square is the other component of the variance (Table 1), which was then divided by:
\[
\frac{(\sum m_i)^2 - \sum m_i^2}{(n - 1) \sum m_i}
\]

where \(m_i\) is the number of observations of a subject \(i\), and \(n\) is the number of subjects. The result of this division was finally summed with the within subjects’ mean square to determine the overall variance. The square root of that overall variance was the standard deviation of the difference.

Table 1. Example of a one-way analysis of variance table produced by SPSS

<table>
<thead>
<tr>
<th></th>
<th>Sum of Squares</th>
<th>df</th>
<th>Mean Square</th>
<th>F</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Between Subjects</td>
<td>4.785</td>
<td>5</td>
<td>0.957</td>
<td>10.761</td>
<td>0.000</td>
</tr>
<tr>
<td>Within Subjects</td>
<td>52.201</td>
<td>587</td>
<td>0.089</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>56.986</td>
<td>592</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*df: degrees of freedom, F: variance of the groups mean; Sig: significance*

The determination coefficient \((r^2)\) between the two methods was calculated with regression analysis and was considered significant when \(P < 0.05\). All statistical analyses were performed on IBM SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp) and GraphPad Prism 6 (GraphPad Prism, Version 6 for Windows, GraphPad Software, La Jolla California, USA).

2.3 Results

The mean ± SD PA temperature was 38.36 °C ± 0.84 °C, and it ranged from 36.30 °C to 40.20 °C. The mean temperature measured by the deep rectally inserted VS capsules (DRVS) was 38.49 °C ± 0.70 °C, and ranged from 37.00 °C to 40.32 °C. The mean difference ± SD was -0.12 °C ± 0.1 °C. The 95% limits of agreement were within -0.32 °C and 0.08 °C (Figure 1).
This means that the VS capsules were overestimating the gold standard by 0.12 °C on average, and that 95% of its readings were not overestimating by more than 0.32 °C or underestimating by less than 0.08 °C the readings of the PA catheter. The coefficient of determination ($r^2$) obtained was 0.88 ($P < 0.0001$) (Figure 2). One pig developed hyperthermia (core temperature $\geq 40$ °C) during anesthesia. The mean difference between the two methods (PA – VS) in this animal was -0.13 °C ± 0.14 °C, and the 95% LoA were -0.39 °C and 0.14 °C.
Figure 1. Bland-Altman plot of body temperature values measured concurrently by pulmonary artery catheters (PA) and VitalSense® capsules (VS) inserted 15 cm deep into the rectum of anesthetized pigs (n = 6). $T_{\text{Avg}}$ is the average between simultaneous readings of the two methods $[(\text{PA}+\text{VS})/2]$ °C and $T_{\text{Diff}}$ is the difference between simultaneous readings of the pulmonary artery (PA) catheter and the VitalSense® capsules (PA-VS) °C. The central solid line represents the mean difference (- 0.12 °C), the upper line represents the upper 95% limit of agreement (0.08 °C), and the lower line represents the lower 95% limit of agreement (- 0.32 °C). The dash line represents a reference for no difference between the methods.
Figure 2. Linear regression plot between the readings of the VitalSense® (VS) capsules and those of the pulmonary artery (PA) catheter in anesthetized pigs (n = 6), in degrees Celsius. The line represents the line of best fit ($r^2 = 0.88; P < 0.0001$).
2.4 Discussion and Conclusions

To the best of my knowledge, this is the first study evaluating rectal placement of VS temperature capsules in animals. The results shown in the present study are very close to the standard established in humans as a clinically acceptable temperature monitoring technique. A mean difference within ± 0.1 °C and 95% LoA within ± 0.4 °C, when comparing a novel method to a gold standard, is considered acceptable for a core temperature monitoring technique in humans (Byrne & Lim 2007). In that study, the authors developed a meta-analysis of the reviewed studies with the objective of re-evaluate the conclusions previously made regarding the accuracy of the use of telemetry pills to monitor core body temperature in humans (Byrne & Lim 2007). In the present study, in spite of a slightly higher mean difference, a narrower range of 95% LoA was obtained, which indicates higher precision.

In the present study, the mean difference between VS capsules and PA temperature readings was lower than the mean difference between rectal and femoral artery temperatures (-0.25 °C ± 0.3 °C) of another study in pigs (Hanneman et al. 2004). Femoral artery temperature was virtually equal to PA temperature in the Hanneman et al. (2004) study. The difference between the results of the two studies may be due to the smaller sample size (n = 2) than that of the present study, and due to the fact that one of the pigs developed hypovolemia during the anesthesia in the study published by Hanneman et al. (2004). The authors advocated that hypovolemia could have caused blood shunting from the rectum to the core which, consequently, affected the final results of that experiment (Hanneman et al. 2004). Cardiac output was not incorporated into the analysis of the present study since I did not observe any discrepancy in the agreement of the two methods in any particular subject.
In critically ill human patients, the mean difference between PA and rectal temperature (measured with an electronic probe inserted 20 cm into the patients rectum) was lower than the one found in the present study (-0.07 °C) (Lefrant et al. 2003). However, the accuracy was four times higher (±0.4 °C), thus the 95% LoA (0.73 °C and -0.87 °C) were also wider than in the present study, in spite of the lower mean difference. This difference between the two studies could be due to the fact that most of the human patients were critically ill, and in cases of hypovolemia, peripheral circulation could have been deviated from the periphery to the core and rectal temperature may have decreased as a result.

Rectal temperature, measured with probes inserted 5 cm into children’s rectum, was inaccurate at determining extreme values of core temperature (Robinson et al. 1998). Similarly, when comparing infrared tympanic thermometer to a handheld digital thermometer in cats, the authors observed that the techniques differed more at febrile temperatures (Kunkle et al. 2004). In the present study I did not observe greater differences between the methods at increased temperatures. However, since hyperthermia was observed in only one animal, it is not possible to confirm that the novel technique is accurate in hyperthermic pigs. Furthermore, I could not evaluate the accuracy of the novel technique in hypothermic values (<36.0 °C), since none of the animals developed hypothermia during the experiment.

Significantly greater differences between PA and oral temperatures were observed in human patients that were endotracheally intubated when compared to those receiving oxygen supplementation via mask and nasal cannula, or to those that were not receiving oxygen supplementation at all (Lawson et al. 2007). This difference could be due to the fact that the oxygen decreased the temperature of the PA by conduction. Even though the pigs were receiving
oxygen supplementation via endotracheal tube in the present study, I did not observe such high
difference between the deep rectal VS readings and the PA temperature.

In conclusion, this study confirmed that deep rectally inserted VS capsules accurately
measure core temperature in anesthetized pigs when inserted 15 cm deep into the rectum. The
advantages of this technique are its ease of application and ability to display and record
temperature data frequently.
CHAPTER 3: EVALUATION OF THE ACCURACY OF DIFFERENT METHODS OF MONITORING BODY TEMPERATURE IN ANESTHETIZED BROWN BEARS

3.1 Background and Objectives

The brown bear (*Ursus arctos*) is classified as a Least Concern species in the IUCN Red List (McLellan et al. 2008). However, there are several, small populations of brown bears that are threatened due to recurrent contact with humans and low numbers of individuals (McLellan et al. 2008). Therefore these populations need to be closely monitored to assure the health and conservation of the species. Handling this species requires chemical immobilization to assure staff’s safety, since procedures like biometric measuring; biological material sampling and radio-collaring cannot be performed in an alert bear. However, when capturing free-ranging wild animals a commonly observed complication is hyperthermia (Cattet et al. 1997; Citino et al. 2001; Goodrich et al. 2001; Fahlman et al. 2008; Meyer et al. 2008; Fahlman et al. 2011). Hyperthermia occurs when there is an increase in body heat production associated with an inability to lose excessive body heat, and it can be life threatening (Simon 1993; Bouchama & Knochel 2002; Sessler 2009).

There is some evidence that handheld rectal thermometers are not an accurate method for core temperature measurement in bears (Cattet et al. 1997). An accurate method of measuring core temperature would allow professionals working with wildlife to better monitor and treat cases of hyperthermia. The VS capsules were originally designed to be swallowed by human patients, since stomach temperature accurately estimates core temperature (McKenzie & Osgood 2004). However, wild animals are required to be anesthetized and gastrically intubated to have these capsules correctly and safely placed in the stomach. The objective of this study was to
compare body temperatures measured by handheld digital thermometer (HDT), deep rectally inserted VS capsules and gastrically inserted VS capsules in anesthetized brown bears. This comparison allows the validation of an easy and feasible technique of measuring core temperature in anesthetized free-ranging brown bears.

3.2 Materials and Methods

The present study was approved by the Animal Care Committee of the University of Calgary (Protocol SHC11R-06). Twenty two sub-adult and adult brown bears of both sexes were captured for ongoing studies of the *Foothills Research Institute Grizzly Bear Program* (FGBP) (n = 9) and the *Scandinavian Brown Bear Project* (SBBP) (n = 13); these bears were immobilized with a combination of zolazepam-tiletamine and xylazine or medetomidine. Within the FGBP the captures occurred in the province of Alberta, Canada in June/2011, May and June/2012 and September/2012. Within the SBBP the captures occurred in the county of Dalarna, Sweden in April and June/2011 and in April and August/2012. For captures within the SBBP the doses used were 3 to 5 mg/kg of zolazepam-tiletamine (Zoletil forte vet., Virbac S.A., Carros, France) and 0.03 to 0.05 mg/kg of medetomidine (Domitor® vet., 1 mg/ml, or Zalopine, 10 mg/ml, Orion Pharma Animal Health, Espoo, Finland), and for captures within the FGBP the doses were 3 to 5 mg/kg of zolazepam-tiletamine and 2 to 4 mg/kg (Telazol®, Fort Dodge Laboratories, Inc., Fort Dodge, IA) of xylazine (Cervizine 300; Wildlife Pharmaceuticals, Inc., Fort Collins, CO). All drugs were injected intramuscularly using a low impact darting system on bears pursued by a helicopter (all bears within SBBP and one bear within FGBP) or captured into culvert traps (16 bears within FGBP) (Figure 3). Heart rate (HR) was monitored through stethoscope auscultation, respiratory rate (RR) was monitored via observation of respiratory
movements and rectal temperature (Rectal Temp) was monitored with a standard HDT (DUOFLEX/PXR, Rexall Brands Corp., Mississauga, Ontario); these parameters were recorded on a monitoring sheet (Appendix B).

Figure 3. Anesthetic drugs being remotely injected in a brown bear captured into a culvert trap within the studies of Foothills Research Institute Grizzly Bear Program.
In order to determine if deep rectal placement of the VS capsules provides an accurate measurement of core temperature in a field situation, the temperature measured by deep rectally inserted capsule (DRVS) was compared with the measurements obtained from gastrically placed capsules (GVS). Following immobilization, one VS core temperature capsule (Capsule Sensor, Mini Mitter Company, Inc., a Respiration, Inc. Company, Murrysville, PA 15668) was inserted 15 cm deep into the animals’ rectum, with a standard applicator (Figure 4), and another capsule was inserted into their stomach via a gastric tube (Figure 5). Gastric placement of the VS capsules was only possible in bears captured within the SBBP, due to animal use protocol restrictions. Both capsules were activated with the VS monitor (VitalSense Monitor, Mini Mitter Company, Inc., a Respiration, Inc. Company, Murrysville, PA 15668); transmission of data begun approximately one minute after activation and occurred remotely approximately every 15 seconds thereafter. At the end of the anesthetic procedure, all bears within both FGBP and SBBP received a dose (five times the dose of medetomidine or 0.2 mg/kg for bears anesthetized with xylazine) of atipamezole (Antisedan® vet., 5 mg/ml, Orion Pharma Animal Health for captures within SBBP or Antisedan®; Novartis Animal Health Canada, Inc., Mississauga, ON, Canada for captures within FGBP) intramuscularly.
Figure 4. Standard applicator (15 cm) for rectal insertion of VitalSense® capsules.

Figure 5. Stomach tube for gastric insertion of VitalSense® capsules in brown bears, with inner diameter of 10 mm and outer diameter of 16 mm.
In the same animal, data from the DRVS and GVS capsules were compared with the temperature measured with a standard HDT (DUOFLEX/PXR, Rexall Brands Corp., Mississauga, Ontario). The temperature was measured with a HDT as often as possible in intervals between five and ten minutes to provide paired data. The HDT was inserted eight centimeters into the bears’ rectum and its tip was directed towards the rectal mucosa of the bear to improve the contact. The temperature was recorded following the audible beep produced by the HDT. At the end of the anesthetic procedure, all the bears within both FGBP and SBBP received an IM dose (five times the dose of medetomidine or 0.2 mg/kg for bears anesthetized with xylazine) of atipamezole (Antisedan® vet., 5 mg/ml, Orion Pharma Animal Health).

The data was downloaded from the VS monitor for each individual bear, an example is shown in Appendix B. Paired data points were included in the analysis once three repeated measurements without a difference greater than 0.05 °C were obtained, to guarantee equilibrium of the capsules’ and the body temperature. Data were analyzed with Bland-Altman technique corrected for repeated measurements in the same subject (Bland & Altman 2007), to compare accuracy and precision of the two methods. The correction consists in incorporating the variance of the differences of each data pair for the same subject and the variance for differences between the averages of the two methods across the subjects on the calculation of the standard deviation of the difference (Bland & Altman 2007), as explained in chapter 2, section 2.2.

Regression analysis was performed to obtain the $r^2$ and determine whether or not the temperature varied between methods in the same fashion. The determination coefficient was also considered significant if $P < 0.05$. All statistical analyses were performed on IBM SPSS 20 (IBM
SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp) and GraphPad Prism 6 (GraphPad Prism, Version 6 for Windows, GraphPad Software, La Jolla California, USA).

To determine if the agreement between the two methods was clinically acceptable, the inherited accuracy of the device considered the gold standard (VitalSense®), given by the manufacturer, was summed to the threshold described by Byrne and Lim (2007) for core temperature monitoring in humans. The accuracy of the VS capsules according to the manufacturer is ± 0.1 °C. The threshold established by Byrne and Lim (2007) for a novel method of monitoring core temperature to be considered clinically acceptable in humans is a mean difference ≤ ± 0.1 °C and the 95 % LoA within ± 0.4 °C. Hence, in this present study, an acceptable agreement between the two methods was considered when the mean difference < ± 0.2 °C and 95 % LoA within ± 0.4 °C. This approach was adapted from Darwent et al. (2011). The data is presented as mean ± standard deviation (range).
3.3 Results

The temperature measured with HDT, DRVS and GVS is summarized in Table 2. The mean HR in beats and RR in breaths per minute were $61.50 \pm 15.17$ (22 to 100) and $9.66 \pm 5.29$ (1 to 46), respectively.

Table 2. Mean ± standard deviation and range of temperatures measured by handheld digital thermometer, gastrically and deep rectally inserted VitalSense® capsules in anesthetized brown bears.

<table>
<thead>
<tr>
<th>Temperature monitor</th>
<th>Mean ± SD</th>
<th>Number of readings</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>HDT</td>
<td>39.29 °C ± 1.02 °C</td>
<td>217</td>
<td>36.50 °C to 40.56 °C</td>
</tr>
<tr>
<td>GVS</td>
<td>37.02 °C ± 2.29 °C</td>
<td>1234</td>
<td>33.44 °C to 40.51 °C</td>
</tr>
<tr>
<td>DRVS</td>
<td>37.48 °C ± 2.05°C</td>
<td>2880</td>
<td>33.42 °C to 41.79 °C</td>
</tr>
</tbody>
</table>


The mean difference and standard deviation of the difference between HDT and GVS (GVS – HDT) readings were $0.27 \pm 0.47 ^\circ C$ and the 95% LoA were $1.2 ^\circ C$ and $-0.66 ^\circ C$ (Figure 6). The two methods had a positive significant correlation: $r^2 = 0.68$ ($P < 0.0001$) (Figure 7). The mean difference and standard deviation of the difference between HDT and DRVS (DRVS – HDT) readings were $0.36 \pm 0.32 ^\circ C$ and the 95% LoA were $1.0 ^\circ C$ and $-0.28 ^\circ C$ (Figure 8). The correlation between these methods was also positive and significant: $r^2 = 0.83$ ($P < 0.0001$) (Figure 9).
Figure 6. Bland-Altman plot of body temperature values measured concurrently by a handheld digital thermometer (HDT) and gastrically inserted VitalSense® capsules (GVS) in anesthetized brown bears (n = 18). $T_{AVG1}$ is the average between simultaneous readings of the two methods $[(HDT+GVS)/2]$ °C and $T_{DIFF1}$ is the difference between simultaneous readings two methods (GVS - HDT) °C. The central line represents the mean difference (0.27 °C), the upper line represents the upper 95% limit of agreement (1.2 °C), and the lower line represents the lower 95% limit of agreement (-0.66 °C). The dash line represents a reference for no difference between the methods.
Figure 7. Linear regression plot between the readings of the gastrically inserted VitalSense® (VS) capsules and those of the handheld digital thermometer (HDT) in anesthetized brown bears (n = 18), in degrees Celsius. The line represents the line of best fit ($r^2 = 0.68; P < 0.0001$).
Figure 8. Bland-Altman plot of body temperature values measured concurrently by a handheld digital thermometer (HDT) and deep rectally inserted VitalSense® capsules (DRVS) in anesthetized brown bears (n = 9). $T_{AVG2}$ is the average between simultaneous readings of the two methods $[\frac{(HDT+DRVS)}{2}]$ °C and $T_{DIFF2}$ is the difference between simultaneous readings two methods (DRVS - HDT) °C. The central line represents the mean difference (0.36 °C), the upper line represents the upper 95% limit of agreement (1.0 °C), and the lower line represents the lower 95% limit of agreement (-0.28 °C). The dash line represents a reference for no difference between the methods.
Figure 9. Linear regression plot between the readings of the deep rectally inserted VitalSense© (VS) capsules and those of the handheld digital thermometer (HDT) in anesthetized brown bears (n = 9), in degrees Celsius. The line represents the line of best fit ($r^2 = 0.83; P < 0.0001$).
When comparing the two insertion methods of the VS capsules (GVS - DRVS), the mean difference and standard deviation of the difference were - 0.15 °C ± 0.36 °C and the 95 % LoA were 0.57 °C and - 0.87 °C (Figure 10). However, on the distribution box plot (Figure 11) I identify some extreme outlier paired samples that belong from the same subject, which was later excluded from the analysis. The values for mean difference and standard deviation of the difference after the exclusion of the outlier markedly reduced to - 0.06 °C ± 0.24 °C and the 95 % LoA of 0.42 °C and - 0.54 °C (Figure 12). The summary of the results of the Bland-Altman analyses are in Table 3. The $r^2$ found between GVS and DRVS after the exclusion of the outlier was 0.91 ($P < 0.0001$) (Figure 13).

**Table 3.** Bland-Altman analysis comparing handheld digital thermometers with deep rectally and gastrically inserted VitalSense® (VS) capsules, and the deep rectally inserted VS capsules with the gastrically inserted VS capsules.

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>$d$ ± SD$_d$</th>
<th>Upper LoA</th>
<th>Lower LoA</th>
<th>$r^2$ ($P$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>GVS$^1$ x HDT$^2$</td>
<td>18</td>
<td>0.36 °C ± 0.32 °C</td>
<td>1.0 °C</td>
<td>- 0.28 °C</td>
<td>0.83 (&lt; 0.0001)</td>
</tr>
<tr>
<td>DRVS$^1$ x HDT$^2$</td>
<td>9</td>
<td>0.27 °C ± 0.47 °C</td>
<td>1.2 °C</td>
<td>- 0.66 °C</td>
<td>0.68 (&lt; 0.0001)</td>
</tr>
<tr>
<td>GVS$^1$ x DRVS$^2$ (with outlier)</td>
<td>8</td>
<td>- 0.15 °C ± 0.36 °C</td>
<td>0.57 °C</td>
<td>- 0.87 °C</td>
<td>0.81 (&lt; 0.0001)</td>
</tr>
<tr>
<td>GVS$^1$ x DRVS$^2$ (without outlier)</td>
<td>7</td>
<td>- 0.06 °C ± 0.24 °C</td>
<td>0.42 °C</td>
<td>- 0.54 °C</td>
<td>0.91 (&lt; 0.0001)</td>
</tr>
</tbody>
</table>

*DRVS: deep rectal VitalSense®; HDT: handheld digital thermometer; GVS: gastric VitalSense®; n: number of bears; d: mean difference (1-2); SD$_d$: standard deviation of the difference; LoA: 95 % limit of agreement; $r^2$: determination coefficient; $P$: significance value.*
Figure 10. Bland-Altman plot of body temperature values measured concurrently by deep rectally (DRVS) and gastrically inserted VitalSense® capsules in anesthetized brown bears (n = 8). $T_{Avg3}$ is the average between simultaneous readings of the two methods [(GVS+DRVS)/2] °C and $T_{Diff3}$ is the difference between simultaneous readings two methods (GVS - DRVS) °C. The central line represents the mean difference (-0.15 °C), the upper line represents the upper 95% limit of agreement (0.57 °C), and the lower line represents the lower 95% limit of agreement (-0.87 °C). The dash line represents a reference for no difference between the methods.
**Figure 11.** Box-plot of the distribution of the differences between the concurrent readings of gastrically (GVS) and deep rectally inserted VitalSense® (DRVS) capsules.
Figure 12. Bland-Altman plot of body temperature values measured concurrently by deep rectally (DRVS) and gastrically inserted VitalSense® capsules in anesthetized brown bears after exclusion of one outlier (n = 7). $T_{Avg4}$ is the average between simultaneous readings of the two methods $[(GVS+DRVS)/2]$ °C and $T_{Diff4}$ is the difference between simultaneous readings two methods $(GVS - DRVS)$ °C. The central line represents the mean difference (- 0.06 °C), the upper line represents the upper 95% limit of agreement (0.42 °C), and the lower line represents the lower 95% limit of agreement (- 0.54 °C). The dash line represents a reference for no difference between the methods.
Figure 13. Linear regression plot between the readings of the gastrically (GVS) and deep rectally inserted VitalSense® capsules (DRVS) anesthetized brown bears (n = 7), in degrees Celsius. The line represents the line of best fit ($r^2 = 0.91; P < 0.0001$).
3.4 Discussion and Conclusions

The results presented previously show that HDT had a greater mean difference and standard deviation of the difference than acceptable in the present study (mean difference within ± 0.2 °C, and 95 % LoA ± 0.4 °C) when compared to core body temperature measured by the gastrically and the deep rectally inserted VS capsules. Even though there is a positive and significant correlation between the readings of the HDT and both insertions of the VS capsules, the agreement between them is not acceptable according to those standards (Byrne & Lim 2007). That means that the HDT could underestimate the core temperature in up to 1.0 °C, which suggests that in case of hyper- or hypothermia, treatment might not be applied when body temperature is being monitored only with a HDT.

The mean difference between the HDT and the gastric temperature found in this study was similar to that in goats (0.4 °C) (Torrao et al. 2011). Contrarily, the SD (± 0.1 °C) and the 95 % LoA (0.2 °C and - 0.6 °C) in that study in goats were lower than that of the present study. The goats’ rectal temperature was measured by a HDT and compared to that measured by a data logger inserted into the abdominal cavity of goats (Torrao et al. 2011). The differences between the two studies can be attributed to the controlled fashion of the study in goats, which might have decreased the variance among the subjects. The goats were fastened, housed in controlled temperature enclosures and they were not anesthetized before temperature monitoring was in place.

When comparing HDT with both deep rectally and gastrically inserted VS capsules, the results of this study were similar to those found in hypovolemic sheep (Mansel et al. 2008). The rectal temperature was measured using thermistor probes inserted 5 cm into the sheep’s rectum; and the core temperature, was measured using a thermistor tipped PA catheter (Mansel et al.
Mansel et al. (2008) concluded that rectal temperature was an accurate method of measuring core temperature in hypovolemic sheep, even though the mean difference was 0.55 °C ± 0.6 °C, and the 95% LoA were 1.75 °C and -0.65 °C. In that case, the HDT could underestimate core temperature in up to 1.75 °C, which would affect the judgement of the staff regarding a clinical intervention in case of hypo- or hyperthermia.

When comparing the readings of the deep rectally to the gastrically inserted VS capsules after the exclusion of the outlier, the mean difference and the standard deviation of the difference showed good agreement between the two methods, very close to the standards established in the present study. The mean difference between the GVS and the DRVS temperatures with the presence of the outlier was not only greater than that found when comparing HDT with GVS, but also, the DRVS overestimated the GVS readings. This overestimation disagrees with the rectal temperatures measured with HDT, which were underestimating the GVS readings. Thus, after analyzing the distribution of the difference between the capsules I observed paired data points deviating extremely from normality (Figure 11). I also observed that all these paired data points belong to the same subject, thus I considered that possibly this animal might have ingested cold water prior to capture. Even though it is not possible to verify this theory, this outlier was removed from the analysis since:

- it provoked such dramatic difference in the final results;
- it appeared as an extreme outlier on the distribution box plot (Figure 11);
- the subject represented only 47 of 436 paired samples.

Since rectal temperature is considered by some authors a gold standard for core body temperature in humans, this technique was used to validate indigestible temperature capsules by
McKenzie and Osgood (2004) and Darwent et al. (2011). In both studies the authors concluded that the capsule readings had good agreement with rectal temperature. The mean differences were $0.04 \degree C \pm 0.03 \degree C$ (with 95 \% LoA of 0.1 $\degree C$ and - 0.02 $\degree C$) and $0.06 \degree C \pm 0.35 \degree C$ (mean difference $\pm$ 95 \% CI), respectively (McKenzie & Osgood 2004; Darwent et al. 2011). These results are similar to those of the present study. In one of these studies the rectal probes were inserted 10 cm into the rectum (Darwent et al. 2011), whereas in the other study the probes were only inserted 11 mm beyond the anal sphincter (McKenzie & Osgood 2004). Thus, the good agreement between the techniques did not depend on the depth of the rectal probe’s insertion in humans. However, in bears, due to size and possible anatomical differences, the depth of insertion of a rectal thermometer could possibly influence the accuracy of the readings.

Rectal temperature measured with HDT inserted 3 cm into dogs’ rectum had good agreement with PA temperature under conditions of normo-, hypo- and hyperthermia (Greer et al. 2007). However, the absolute values of mean difference and standard deviation of the difference were not reported (Greer et al. 2007). The results of the present study disagree with the study in dogs, regarding the agreement between the readings of HDT and the core temperature. Size might be one of the reasons why HDT did not accurately estimate core temperature in bears, as deep rectal readings of VS capsules agreed well with those inserted in the bears’ stomach. A better agreement could be possible with the use of a longer HDT that could be inserted 15 cm into the bears’ rectum (as with the VS capsules), instead of only 8 cm. However, a longer HDT would not have the advantage of continuous and remote monitoring that the VS monitor provides.

In the present study, good agreement between deep rectally and gastrically inserted VS capsules was found in a wide range of gastric temperature ($33.44 \degree C$ to $40.51 \degree C$). However,
during extreme rates of exercise, the VS capsules did not seem to reflect esophageal temperature in humans and the authors concluded that it is not a reliable technique to monitor core temperature in that situation (Teunissen et al. 2012). The statistical analysis performed on that study was analysis of variance, which is not the recommended approach to compare methods, as described by (Bland & Altman 1999).

One limitation of the present study was the fact that I could not perform the experiments in yearling bears due to size restriction. It would not be possible to fit the stomach tube with the necessary diameter to fit a VS capsule inside it in smaller bears. In these smaller bears, like in dogs (Greer et al. 2007), a better agreement between HDT and GVS could have been possibly observed, due to their similar sizes. Another limitation of the present study was that, due to animal use protocol restrictions, only animals within the SBBP captures had a VS capsule inserted into their stomachs. If a wider and more heterogeneous population was included in the three comparisons and not only in two, a different variability might have been found.

In conclusion, this study shows that deep rectally inserted VS capsules accurately measure core temperature in anesthetized brown bears and that HDT does not accurately estimate core temperature in anesthetized brown bears. The HDTs will still reflect the trend in temperature over time. However it can underestimate core temperature in up 1.0 °C and this must be kept in mind when considering at what temperature to diagnose and treat hyperthermia. When capturing bears, their temperature is commonly monitored rectally with HDTs and knowing that hyperthermia is a life threatening situation, the results found in the present study will be useful for researchers working with bear capture by increasing their level of awareness regarding the limitations of the techniques to monitor body temperature. It is also possible to conclude that DRVS capsules accurately measure core temperature in anesthetized brown bears. The
advantages of this technique are its ease of operation, feasibility to field conditions and continuous real-time monitoring.
CHAPTER 4: EVALUATION OF THE EFFECTIVENESS OF ACTIVE COOLING AND ALPHA-2 ANTAGONISM TO DECREASE CORE TEMPERATURE IN ANESTHETIZED BROWN BEARS

4.1 Background and Objectives

Hyperthermia is a common complication during bear anesthesia (Bush et al. 1980; Lee et al. 1981; Hellgren & Vaughan 1989; Stirling et al. 1989; Taylor et al. 1989; White et al. 1996; Cattet et al. 1997). Forty-six percent of free-ranging brown bears (*Ursus arctos*) captured following helicopter pursuit, with a combination of medetomidine-zolazepam-tiletamine developed hyperthermia (Fahlman et al. 2011). In contrast, none of the six captive brown bears, anesthetized with the same drug combination, developed hyperthermia (Fahlman et al. 2011). In that study, the hyperthermia in free-ranging brown bears (*U. arctos*) could be related to the physical exertion following helicopter pursuit. Hyperthermia (*Tb = 40.1 °C*) in one of 14 captive bears of different species was reported on the two occasions in which the same animal was anesthetized using a combination of phencyclidine and promazine (Bush et al. 1980). One polar bear (*Ursus maritimus*) died due to hyperthermia even after administration of two cold water enemas and one IV dose of atipamezole (Cattet et al. 1997). Two black bears (*Ursus americanus*) anesthetized after snare capture also died due to hyperthermia, one of them with an extremely high body temperature of 43.0 °C (Hellgren & Vaughan 1989).

Treatments for hyperthermia reported in humans and animals include external cooling, cold water enemas, IV fluids administration and oxygen supplementation (Deem & Karesh 2001; Foster 2005; Fahlman et al. 2010; Sawicka 2010; Williamson et al. 2010; Arnemo et al. 2011; Fahlman et al. 2011). However, depending on the field work conditions, these treatments may
not always be feasible because they depend on equipment that might be difficult to transport. The best method for cooling hyperthermic human athletes is considered to be cold water immersion (Casa et al. 2007; DeMartini et al. 2011). Hyperthermic athletes are immersed in a bath with cold water and ice, which would not be feasible for a large animal like a bear captured in the field. Other methods like circulating cold water or ice pack vests were developed specifically for human use (DeMartini et al. 2011) and are not anatomically compatible with brown bears. Immersion in water can be possible if the capture happens close to a natural water source, like a river or lake, as described by Taylor et al. (1989). Other reported cooling methods used to treat hyperthermic bears include cold water enemas (Cattet et al. 1997), external cooling with water (Hellgren & Vaughan 1989), intranasal oxygen supplementation (Fahlman et al. 2010) and placement of snow or wet moss in the bears’ pads and groins (Taylor et al. 1989). However, to my knowledge, there are no studies evaluating the effectiveness of these treatments in bears and few studies have evaluated cooling methods in other wild mammal species (Sawicka 2010).

It is known that the use of the alpha-2 agonist clonidine impairs thermoregulation promoting central thermogenesis in guinea pigs, which increases the body heat production (Feleder et al. 2004). These drugs also promote peripheral vasoconstriction (Maze & Tranquilli 1991), which hampers loss of the excessive body heat (Flavahan 1991). However, it has been demonstrated in bears that combinations of alpha-2 agonists and zolazepam-tiletamine are effective, safe, have analgesic properties and allow the use of low impact darting systems (due to lower volume of drugs). Moreover, another advantage of these protocols in bears is that alpha-2 agonists can be antagonized (Caulkett et al. 1999; Cattet et al. 2003a; Cattet et al. 2003b). In one reported case, atipamezole did not succeed when used to antagonize the medetomidine in an attempt to treat a hyperthermic polar bear (*Ursus maritimus*) that did not respond to two cold
water enemas (Cattet et al. 1997). However, to my knowledge there are no studies evaluating the use of atipamezole to treat alpha-2 agonist-related hyperthermia in bears.

The objective of the present study was to evaluate the core body temperature decrease produced by an active cooling protocol and by alpha-2 antagonism; and also, to compare rectal to core temperature during the active cooling protocol, to determine if rectal thermometry it is an adequate technique to monitor temperature in this situation.

4.2 Materials and Methods

This study was approved by the Animal Care Committee of the University of Calgary (Protocol SHC11R-06). Twenty-five adult and sub adult brown bears that were captured for the ongoing studies of the FGBP (n = 13) and the SBBP (n = 12) were included in this study. Within the FGBP, bears were captured using culvert traps and darted in the trap using a low impact darting system, with a combination of zolazepam-tiletamine (3 to 5 mg/kg IM) (Telazol®, Fort Dodge Laboratories, Inc., Fort Dodge, IA) and xylazine (2 to 4 mg/kg IM) (Cervizine 300; Wildlife Pharmaceuticals, Inc., Fort Collins, CO). There was only one exception in the captures within the FGBP, a bear that was darted from a helicopter, using the same darting system and drug combination. For captures within the SBBP all bears were darted from a helicopter using a low impact darting system with an anesthetic combination of zolazepam-tiletamine (3 to 5 mg/kg IM) (Zoletil forte vet., Virbac S.A., Carros, France) and medetomidine (0.03 to 0.05 mg/kg IM) (Domitor® vet., 1 mg/ml, or Zalopine, 10 mg/ml, Orion Pharma Animal Health, Espoo, Finland).

At the end of the anesthetic procedure, all bears within both FGBP and SBBP received a dose (five times the dose of medetomidine or 0.2 mg/kg for bears anesthetized with xylazine) of atipamezole (Antisedan® vet., 5 mg/ml, Orion Pharma Animal Health for captures within SBBP.
or Antisedan®; Novartis Animal Health Canada, Inc., Mississauga, ON, Canada for captures within FGBP) intramuscularly. Within the FGBP the captures occurred in the province of Alberta, Canada; in June/2011, May and June/2012 and September/2012. Within the SBBP the captures occurred in the county of Dalarna, Sweden; on April and June/2011; and in April and August/2012.

Within captures of SBBP one VS capsule (Capsule Sensor, Mini Mitter Company, Inc., a Respironics, Inc. Company, Murrysville, PA 15668) was inserted into the bears’ stomach via stomach tube (Figure 5) following chemical immobilization. Another VS capsule was inserted 15 cm deep into the animal’s rectum with a standard applicator (Figure 6). Both capsules were activated with the VS monitor (VitalSense Monitor, Mini Mitter Company, Inc., a Respironics, Inc. Company, Murrysville, PA 15668) and data transmission began approximately one minute after activation and occurred approximately every 15 seconds thereafter. In the captures within FGBP only one VS capsule was inserted 15 cm into the rectum also with a standard applicator. Every five to ten minutes, rectal temperature was measured in all subjects with a HDT (Mansfield Medical Distributors, LTD., Montreal, Quebec) inserted 8 cm into the animal’s rectum and recorded in the monitoring sheet (Appendix 1). The tip of the HDT was directed to the rectal mucosa of the bear to ensure contact. The temperature was recorded after the device produced an audible beep.

In bears that demonstrated gastric temperatures greater or equal to 40 °C active cooling protocol was performed by applying all of the following treatments until gastric temperature was lower than 40 °C (or until the end of the anesthetic procedure):
- Enemas with 2 L of water at 4 °C to 6 °C per 100 kg of body weight, every ten minutes;

- IV fluid at a rate of 40 mL/kg/hour;

- External cooling by applying water or snow (depending on the availability) on the paws and in the inguinal area;

- Intranasal oxygen supplementation at 1 to 3 L/minute, depending on the size of the bear, according to the optimal flow for oxygen supplementation in brown bears as described by (Fahlman et al. 2010);

- Removing the bear from direct sun light.

This active cooling protocol was adapted from what is currently used within SBBP and from recommendations published as guidelines for different species (Deem & Karesh 2001; Foster 2005; Arnemo et al. 2011). Temperatures were analyzed graphically to observe the temperatures measured with HDT and DRVS capsules in contrast to core temperature (measured with GVS capsules) during the active cooling process, considering that the animals’ recta were flushed with cold water.

The effect of active cooling on the core temperature was determined by analyzing the temperature change measured by GVS capsules every five minutes for 30 minutes after start of the active cooling protocol (Time 0). The temperature change was calculated by subtracting the gastric temperatures at Times 5, 10, 15, 20, 25 and 30 minutes after the start of active cooling, from the gastric temperature at Time 0. Six bears were included in this group and they were all
captured within the studies of the SBBP. This group was designated as the *Active Cooling Group* (Group AC).

To determine if antagonism of the alpha-2 agonist decreased core body temperature of anesthetized brown bears, the change in temperature monitored by DRVF capsules was analyzed every five minutes for 30 minutes after the administration of IM atipamezole. The VS monitor was encased in a protective case and placed close (< 1 m) to the recovering bear (Figure 14), to allow continuous monitoring of deep rectal temperature until the animal left the area. The temperature change was calculated by subtracting the deep rectal temperatures at Times 5, 10, 15, 20, 25 and 30 minutes after administration of atipamezole (Time 0), from the deep rectal temperature at Time 0. The ten bears included in this analysis were captured within the ongoing studies of the FGBP only, for logistical purposes. Since the FGBP capture staff inspected the capture area 24 hours after every capture, I was able to leave the VS monitor after the end of the anesthesia and return the following day to retrieve it. This group was designated as the *Atipamezole Group* (Group A).
Figure 14. Enclosed VitalSense® monitor left near a brown bear recovering from anesthesia.

Nine bears that did not receive active cooling treatment had their temperatures evaluated for 30 minutes following chemical immobilization, prior to administration of atipamezole. The nine bears included in this analysis were captured within both FGBP and SBBP. The bears captured within the FGBP (n = 3) had one VS capsule inserted 15 cm deep into the rectum and the temperatures were analyzed for 30 minutes after stabilization of the readings. That is, whenever the VS capsules recorded three consecutive measurements that did not vary more than 0.05 °C. The bears captured within the SBBP (n = 6) had one VS capsule inserted into the stomach and its readings were analyzed for 30 minutes after stabilization of readings, as previously described. The temperature change was calculated subtracting the deep rectal temperatures at Times 5, 10, 15, 20, 25 and 30 minutes after beginning the monitoring (Time 0), from the deep rectal temperature at Time 0. This group was called the Control Group (Group C).
The choice of the time frame for the analyses (30 minutes) was based on the dataset obtained. That is, 30 minutes was the maximum period of data obtained that was common to the three different groups. To compare the differences in temperature change among the groups the area under the curve (AUC) of temperature change over time was calculated for each individual bear. Following, the AUCs obtained were analyzed with one-way analysis of variance (ANOVA). To evaluate the body temperature trend over time within each group, the change in temperature for each time point was compared to Time 0 with a General Linear Model for Repeated Measures (RM-GLM) with Tukey’s Post Hoc test. A difference was considered statistically significant for all analyses when \( P < 0.05 \).

In all groups other variables were recorded: HR, determined through stethoscope auscultation; RR, determined via observation of respiratory movements; ambient temperature, recorded with an ambient thermometer; anesthetic time, defined as the time from darting until administration of the antagonist; and body weight in kilograms (kg). To determine if body temperature at Time 0, ambient temperature, anesthetic time and body weight were have influenced on the temperature variation among the groups, a one-way ANOVA with Tukey’s Post hoc test, was performed. The differences among groups were considered significant when \( P < 0.05 \). All statistical analyses were performed with IBM SPSS 20 (IBM SPSS Statistics for Windows, Version 20.0, Armonk, NY: IBM Corp) and GraphPad Prism 6 (GraphPad Prism, Version 6 for Windows, GraphPad Software, La Jolla California, USA). The data is presented as mean ± standard deviation (range).
4.3 Results

The ambient temperature during the capture of the bears in Group AC was 14.5 °C ± 8.6 °C (5.0 °C to 26.2 °C); in Group A was 6.3 °C ± 3.9 °C (3.0 °C to 11.0 °C) and in Group C was 9.1 °C ± 3.0 °C (5.0 °C to 12.4 °C). The anesthetic time (minutes) in Group AC was 149 ± 30.1 (121 to 178); in Group A was 144.3 ± 14.0 (133 to 160) and in Group C was 132.5 ± 26.6 (100 to 165). The temperatures at Time 0 and at Time 30 in the three different groups are summarized in Table 4 and the summary of the body weight for each individual in the different groups is summarized in Table 5, no significant differences were observed among the groups. Mean HR and RR in Group C were: 67.73 ± 11.60 beats per minute and 7.87 ± 3.60 breaths per minute; in Group AC: 61.31 ± 17.75 beats per minute and 12.97 ± 8.20 breaths per minute; and in Group A: 70.30 ± 10.80 beats per minute and 10.86 ± 3.76 breaths per minute.

Table 4. Mean ± standard deviation (range) body temperature measured with gastrically and deep rectally inserted VitalSense® capsules in the different groups of anesthetized brown bears (n = 29).

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Mean ± SD (range) at Time 0</th>
<th>Mean ± SD (range) at Time 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>AC</td>
<td>6</td>
<td>40.59 °C ± 0.38 °C (40.16 °C to 41.28 °C)</td>
<td>39.58 °C ± 0.67 °C (38.65 °C to 40.39 °C)</td>
</tr>
<tr>
<td>A</td>
<td>10</td>
<td>38.70 °C ± 1.52 °C (36.09 °C to 41.79 °C)</td>
<td>38.14 °C ± 1.62 °C (35.24 °C to 41.21 °C)</td>
</tr>
<tr>
<td>C</td>
<td>9</td>
<td>39.97 °C ± 0.42 °C (39.18 °C to 40.51 °C)</td>
<td>39.71 °C ± 0.49 °C (38.78 °C to 40.35 °C)</td>
</tr>
</tbody>
</table>

AC: Group Active Cooling; A: Group Atipamezole and C: Group Control; n: number of subjects.
**Table 5.** Individual and mean ± SD body weight (Kg) values in the different groups of anesthetized brown bears.

<table>
<thead>
<tr>
<th>Group</th>
<th>Bear</th>
<th>Capture Location</th>
<th>Sex</th>
<th>Individual Body Weight (kg)</th>
<th>Mean ± SD Body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1</td>
<td>Sweden</td>
<td>Female</td>
<td>52.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Sweden</td>
<td>Female</td>
<td>49.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Sweden</td>
<td>Male</td>
<td>207</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Sweden</td>
<td>Male</td>
<td>100</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Canada</td>
<td>Female</td>
<td>94.5</td>
<td>109.94 ± 57.02</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Canada</td>
<td>Male</td>
<td>193.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Canada</td>
<td>Female</td>
<td>132.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Sweden</td>
<td>Female</td>
<td>73</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Sweden</td>
<td>Female</td>
<td>87</td>
<td></td>
</tr>
<tr>
<td>Active Cooling</td>
<td>1</td>
<td>Sweden</td>
<td>Male</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Sweden</td>
<td>Female</td>
<td>67</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Sweden</td>
<td>Male</td>
<td>230</td>
<td>91.67 ± 68.25</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Sweden</td>
<td>Female</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Sweden</td>
<td>Female</td>
<td>66.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Sweden</td>
<td>Female</td>
<td>49.5</td>
<td></td>
</tr>
<tr>
<td>Atipamezole</td>
<td>1</td>
<td>Canada</td>
<td>Female</td>
<td>88.6</td>
<td>119.85 ± 50.47</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Canada</td>
<td>Female</td>
<td>94.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Canada</td>
<td>Female</td>
<td>99</td>
<td></td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Canada</td>
<td>Female</td>
<td>116</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Canada</td>
<td>Female</td>
<td>86.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Canada</td>
<td>Male</td>
<td>113</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>Canada</td>
<td>Female</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Canada</td>
<td>Male</td>
<td>198</td>
<td></td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Canada</td>
<td>Male</td>
<td>193.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Canada</td>
<td>Female</td>
<td>104.4</td>
<td></td>
</tr>
</tbody>
</table>

Initial temperatures differed significantly between Group A and Group C (mean difference = 1.83; \( P = 0.0002 \)), and between Group AC and Group A (mean difference = 2.45; \( P < 0.0001 \)). No statistical difference was observed between Group AC and Group C (mean difference = 0.61; \( P = 0.41 \)). Ambient temperature did not differ significantly among the three
groups (F = 1.35; P = 0.31). Similarly, no significant differences were observed when comparing the anesthetic times among the different groups (F = 0.44; P = 0.66).

When comparing the AUCs among the three different groups no significant difference was observed between Group AC and Group A (mean difference = 7.60; P = 0.068) or between Group A and Group C (mean difference = -5.25; P = 0.22). A significant difference was observed between Group AC and Group C (mean difference = -12.84; P = 0.002) (Figure 15). The mean and SD area under the curve for the different groups is illustrated in Figure 16.

When analyzing the temperature over time in each group, the RM-GLM showed significant change in temperature all groups in comparison to Time 0. In Group C temperature increased significantly at Time 5 (mean difference = -0.61; P = 0.03), and decreased significantly at Times 25 (mean difference = 0.21; P = 0.09) and 30 (mean difference = 0.28; P =0.03) (Figure 17). In Group AC temperature decreased significantly at Times 10 (mean difference = 0.41; P =0.05), 15 (mean difference = 0.57; P =0.03), 20 (mean difference = 0.78; P = 0.01), 25 (mean difference = 0.88; P = 0.02) and 30 (mean difference = 1.0; P = 0.02) (Figure 18). In Group A temperature decreased significantly at Times 5 (mean difference = 0.23; P = 0.02), 10 (mean difference = 0.39; P = 0.01), 15 (mean difference = 0.47; P = 0.01), 20 (mean difference = 53; P = 0.01), 25 (mean difference = 0.61; P = 0.01) and 30 (mean difference = 0.68; P = 0.01) (Figure 19).
Figure 15. Mean and standard deviation of the temperature change for each time point, in degrees Celsius for each group of anesthetized brown bears (n = 29). No significant difference was found between Group AC and Group A (mean difference = 7.28; $P = 0.08$) or between Group A and Group C (mean difference = -5.57; $P = 0.17$). A significant difference was observed between Group AC and Group C (mean difference = -12.85; $P = 0.002$).
Figure 16. Mean and SD of the area under the curve (AUC) in degree Celsius of temperature change x time in minutes; for Groups Control, Active Cooling and Atipamezole. Groups with different symbols (* or †) were significantly different from each other.
Figure 17. Mean and standard deviation of body temperature change measured with deep rectally and gastrically inserted VitalSense® capsule (degrees Celsius) in anesthetized brown bears within the Group Control (n = 9). The asterisks represents the time points that were significantly different than Time 0.
Figure 18. Mean and standard deviation of gastric temperature change (degrees Celsius) in anesthetized brown bears within the Group Active Cooling (n = 6). The asterisks represents the time points that were significantly different than Time 0.
Figure 19. Mean and standard deviation of deep rectal temperature change (degrees Celsius) in anesthetized brown bears within the Group *Atipamezole* (*n* = 14). The asterisks represent the time points that were significantly different than Time 0.
Two of six bears within Group AC remained hyperthermic 30 minutes after the start of the active cooling protocol. One of these bears had a stomach temperature of 40.57 °C before start of active cooling. Even after administration of two cold water enemas, placement of snow in its inguinal area, oxygen supplementation, and 500 ml of IV fluids, the stomach temperature remained above 40°C (40.25 °C 30 minutes after start of active cooling protocol). At the end of the anesthetic procedure, this bear received a dose of atipamezole IM that promoted a decrease in the stomach temperature to 38.94 °C (30 minutes after administration of alpha-2 antagonist) (Figure 20). The other bear that remained hyperthermic (GVS temperature = 40.17 °C) after 30 minutes of administration of active cooling had the temperature continuously decreasing after 30 minutes until values < 40.0 °C and after administration of atipamezole, the temperature trend seemed unchanged.

One bear in Group A, had low deep rectal temperature (35.80 °C) at the time of atipamezole administration. Thirty minutes after administration of atipamezole, the subject’s temperature had increased to 36.14 °C (Figure 22). Another bear had initial HDT temperature (after chemical immobilization) of 42.6 °C. The capture team of the SBBP immersed the bear in water (except the head), in a natural water source close to the capture site. After that, the bear received cold water enemas almost continuously, oxygen supplementation and IV fluids. Due to the extremely high body temperature, the different treatments were initiated urgently, and the GVS capsule was placed 10 minutes after the start of the active cooling. The stomach temperature of this bear over time is presented on Figure 23. Since the active cooling protocol, as described in this chapter, was not followed for this particular bear, it was not included in the analysis.
**Figure 20.** Gastric temperature in degrees Celsius in one anesthetized brown bear during and after active cooling protocol and administration of atipamezole. The dash line represents the time of atipamezole administration (Atp).
Figure 21. Gastric temperature in degrees Celsius in one anesthetized brown bear during and after active cooling protocol and administration of atipamezole. The dash line represents the time of atipamezole administration (Atp).
Figure 22. Deep rectal temperature in degrees Celsius in one anesthetized brown bear before and after administration of atipamezole. The dash line represents the time of atipamezole administration (Atp).
Figure 23. Gastric temperature in degrees Celsius in one anesthetized brown bear that received cold water enema almost continuously, as part of an active cooling protocol.

Another important observation of the present study was that during the active cooling that included cold water enemas, rectal temperature measured by HDT and DRVS capsules was not an adequate core temperature monitoring technique, since the animals’ rectum was flushed with cold water (Figure 24, Figure 25, Figure 26). This is especially important for professionals working with bear capture, because rectal temperature is commonly used for temperature monitoring during anesthesia and also during active cooling, in hyperthermic animals.
Figure 24. Temperatures measured by handheld thermometer (HDT), deep rectally (DRVS) and gastrically inserted (GVS) VitalSense® capsules in one anesthetized brown bear during active cooling with cold water enemas, oxygen supplementation, intravenous fluids and external cooling. The dash lines represent the time of administration of a cold water enema.
Figure 25. Temperatures measured by handheld thermometer (HDT), deep rectally (DRVS) and gastrically inserted (GVS) VitalSense® capsules in one anesthetized brown bear during active cooling with cold water enemas, oxygen supplementation, intravenous fluids and external cooling. The dash lines represent the time of administration of a cold water enema.
Figure 26. Temperatures measured by handheld thermometer (HDT), deep rectally (DRVS) and gastrically inserted (GVS) VitalSense® capsules in one anesthetized brown bear during active cooling with cold water enemas, oxygen supplementation, intravenous fluids and external cooling. The dash line represents the time of administration of a cold water enema.
4.4 Discussion and Conclusions

The results of the present study show showed a statistically significant decrease in temperature in brown bears in all groups. However, atipamezole produced a faster change in body temperature when compared to the active cooling protocol, which is clinically more valuable. In Group C, on its turn, temperature decrease significantly only after 25 minutes of monitoring. Nevertheless, the temperature decrease after 30 minutes produced by active cooling was greater than by atipamezole (mean differences = 1.0 °C and 0.68 °C, respectively).

It is important to emphasize that the initial temperature was significantly lower in Group A in comparison to Group AC, which might have influenced the degree of temperature decrease. Since Group AC had higher initial temperature, the temperature change observed in this group might be related to this initial hyperthermia which was not observed in the Group A. Moreover, the subjects included in Group AC had their abdominal cavities opened for implantation of different devices for study purposes within the SBBP. The surgical incisions were 5 to 10 cm long and the influence of abdominal surgery on heat loss in these bears is unknown.

In spite of a lack of significant difference in the overall temperature change between Groups AC and A, there was a tendency to a difference among these groups ($P = 0.07$). Significant differences among these groups could have been observed with increased power. In the present study, power was affected by the different and small sample sizes of the groups. When calculating the sample size for repeated measures ANOVA with three groups, which would be the ideal statistical approach to this study design, with a power of 0.9 and an effect size of 0.5, a sample size of 11 animals per group was found to be ideal. This sample size was found using the software G*Power (Faul et al. 2007). The power found for each group on the RM-GLM is in Table 6.
Table 6. SPSS output table with values of observed power within each group when evaluating temperature change over time.

<table>
<thead>
<tr>
<th>Group</th>
<th>Mauchy’s sphericity (Significance)</th>
<th>Source</th>
<th>Mean Square</th>
<th>F</th>
<th>Significance</th>
<th>Observed Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.000 (0.000)</td>
<td>Time</td>
<td>.130</td>
<td>15.497</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sphericity Assumed</td>
<td>.447</td>
<td>15.497</td>
<td>0.001</td>
<td>0.991</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Greenhouse-Geisser</td>
<td>.342</td>
<td>15.497</td>
<td>0.000</td>
<td>0.998</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Huynh-Feldt</td>
<td>.780</td>
<td>15.497</td>
<td>0.006</td>
<td>0.919</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower-bound</td>
<td>.681</td>
<td>11.215</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td>Active Cooling</td>
<td>0.000 (0.000)</td>
<td>Time</td>
<td>2.698</td>
<td>11.215</td>
<td>0.011</td>
<td>0.868</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sphericity Assumed</td>
<td>1.822</td>
<td>11.215</td>
<td>0.003</td>
<td>0.962</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Greenhouse-Geisser</td>
<td>4.086</td>
<td>11.215</td>
<td>0.029</td>
<td>0.709</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Huynh-Feldt</td>
<td>.328</td>
<td>15.506</td>
<td>0.000</td>
<td>1.000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Lower-bound</td>
<td>1.394</td>
<td>15.506</td>
<td>0.004</td>
<td>0.958</td>
</tr>
<tr>
<td>Atipamezole</td>
<td>0.000 (0.000)</td>
<td>Time</td>
<td>1.093</td>
<td>15.506</td>
<td>0.001</td>
<td>0.986</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sphericity Assumed</td>
<td>1.966</td>
<td>15.506</td>
<td>0.011</td>
<td>0.878</td>
</tr>
</tbody>
</table>

After administration of atipamezole in the only hypothermic bear, body temperature stopped decreasing and started to increase. Since it is known that alpha-2 agonists can also cause hypothermia (Jalanka & Roeken 1990), the results found in this hypothermic bear suggest that atipamezole might not decrease the absolute body temperature, but it may normalize thermoregulation impaired by alpha-2 agonists instead.
In Group C the temperature trend was different to other reports in polar and grizzly bears anesthetized with zolazepam-tiletamine alpha-2 combinations (Cattet et al. 2003a; Cattet et al. 2003b). In those studies, body temperature increased over 60 minutes of anesthesia. However, the temperature variation of the present study was similar to that found in dogs (Pypendop & Verstegen 2008), rats (MacDonald et al. 1988), American martens (Belant 2005), sun bears (Onuma 2003) and red foxes (Bertelsen & Villadsen 2009). Since some individuals in Group C in the present study were not darted from a helicopter, they did not have the increase in metabolic heat production caused by intense physical activity. This increased body heat production associated with vasoconstriction induced by alpha-2 agonists, most likely prevented body heat loss and caused an increase in body temperature over time in free-ranging polar and grizzly bears (Cattet et al. 2003a; Cattet et al. 2003b). This pattern was not observed in Group C of the present study, probably because there was no initial increase in metabolic heat production in 3 of 9 subjects. Furthermore, the initial temperature in Group C was statistically similar to that in Group AC, which was composed by hyperthermic bears. Thus, an initial high temperature could be another reason why the temperature of Group C decreased over time.

Ambient temperature recorded in the present study did not differ significantly among the three groups, thus it is not possible to determine how this variable might impact the temperature variation in each group. However, in the present study ambient temperatures did not exceed previously published recommendations for bear capture (Cattet et al. 1997), with one exception of an animal captured in an ambient temperature of 26.2 °C. When snare-capturing black bears and further anesthetizing them with ketamine and xylazine in ambient temperatures up to 35 °C, the bears’ rectal temperatures reached up to 43 °C (Hellgren & Vaughan 1989). The
average anesthetic time in the present study was similar to those reported by other authors (Cattet et al. 1997; Asano et al. 2007).

The decrease in temperature produced by the active cooling protocol in the present study was not as substantial as that found by Lagina et al. (2012) in sedated rats. These authors adapted a veterinary warming blanket to have circulating cold water instead of warm water and were able to effectively produce decrease in brain temperature in up to approximately 5 °C in sedated rats within 30 minutes of cooling (Lagina et al. 2012). However, these cooling blankets cannot be used in larger animals, since they are manufactured only for small animals. Moreover, this method is not feasible for field anesthesia since they depend on a continuous source of cold water and electricity. It is important to mention that the initial temperature of the rats was 37.0 °C and the method was developed with the objective of creating a model of therapeutic hypothermia (Lagina et al. 2012) and not to treat hyperthermia as in the present study.

Even though the active cooling protocol significantly decreased the core temperature in the present study, this decrease was also considerably lower than that promoted by whole body immersion in water-ice mixture described by Plattner et al. (1997). These authors observed in anesthetized humans a decrement in tympanic membrane temperature of 9.7 °C ± 4.4 °C per hour (Plattner et al. 1997). However, the same authors observed a temperature drop following treatment with cold water immersion for up to 20 minutes after the end of the immersion, in spite of the use of active rewarming with forced warm air (Plattner et al. 1997).

Gastric lavage was the closest treatment to cold water enema evaluated in the current literature, to the best of my knowledge. In anesthetized dogs, gastric lavage was considered effective on hyperthermic subjects and no post-anesthetic side effects or post-mortem gastric injuries were reported (Syverud et al. 1985). Gastric lavage was considered failed to cool one
anesthetized human patient since the authors were not able to aspirate back the full content of the lavage, which provoked considerable diarrhea and gastrointestinal discomfort (Plattner et al. 1997). Moreover, no significant decrease in temperature was observed with that treatment, which was not repeated in other subjects due to the adverse effects aforementioned (Plattner et al. 1997). Cold water enemas may have produced similar adverse effects in the bears of the present study. However, it is not possible to evaluate such subjective effect as gastrointestinal discomfort in bears, and for safety reasons, it was not possible to observe the bears recovering from anesthesia to detect if they developed diarrhea.

Body condition can also affect the ability of heat loss of an individual. The higher the total body fat content, the longer it takes to decrease body temperature with active cooling in anesthetized human patients (Jimmink et al. 2008). In the present study, none of the captured bears had extreme body conditions, thus, it was assumed that heat loss variations due to body condition was not a variable influencing the study results. However, it is important to emphasize that if there were any bears within the Group AC captured in the fall they would most likely have a higher fat content than those captured in the spring and summer, which could affect the effectiveness of the active cooling protocol.

To the best of my knowledge, this is the first study evaluating an active cooling protocol that includes administration of cold water enemas in wild animals. Other methods of active cooling were evaluated in hyperthermic wild antelopes (Sawicka 2010). The treatments tested were: water dousing at different temperatures (4 °C, 17 °C and 28 °C), water dousing at 28°C with fanning, fine mist spray at 28 °C, 1 L of IV saline at 4°C and placement of ice packs on their skin (Sawicka 2010). The most effective method was considered water dousing irrespective of the water temperature (Sawicka 2010).
The first limitation of this study was the fact that it was not possible to evaluate the treatment with atipamezole in hyperthermic brown bears. The absence of hyperthermic bears in Group A could have influenced the degree of temperature decrease promoted by atipamezole in the present study. However, evidence was found in the one bear with lower body temperature in this study that atipamezole normalizes thermoregulation impaired by alpha-2 agonists, instead of decreasing body temperature *per se*. According to personal opinion of an experienced researcher, a normal value of body temperature in unstressed anesthetized bears ranges from 37 °C to 38 °C.

Another limitation of the present study was that only bears captured within SBBP were treated with cold water enemas. Thus, the present study might be reflecting differences between these two populations instead of the differences between the two treatments. Finally, another limitation was the occurrence of data loss on the VitalSense® monitor. Even though it did not affect the real-time monitoring of temperature during the anesthetic procedure, the missing data points resulted in loss of power on the statistical analysis and it did not allow the use of repeated measures ANOVA with a more robust *Post Hoc* test. In order to adjust the data set to these missing values the area under the curve was calculated for each individual and a one-way ANOVA was then performed. To be able to use this statistical approach, 11 bears per group would be necessary in order to obtain a power of 0.9 and observe an effect size of 0.5 (Faul et al. 2007). However, this is difficult to obtain especially in Group AC, since this comparison depends on the occurrence of a random effect as hyperthermia.

The results of this study show that the active cooling protocol used in hyperthermic bears significantly decreased body temperature of hyperthermic bears after 10 minutes. Alpha-2 antagonist produced an earlier significant decrease but the final change in temperature (at Time 30) was lower than in Group AC. However, no significant difference was found between the
areas under the curves of Groups AC and A. It was not possible to compare the effectiveness to treat hyperthermia of the active cooling protocol with the alpha-2 antagonism, since the subjects of Group A were not hyperthermic. Thus, the temperature variation observed in Group A following administration of atipamezole may not reflect the true temperature variation that this drug would produce in hyperthermic bears. These data also suggest that atipamezole might not reduce core temperature *per se*, but it may normalize thermoregulation impaired by alpha-2 agonists, as observed in the only hypothermic subject of Group A.
CHAPTER 5: SUMMARY

“Was the porridge too hot, too cold or just right?”

5.1 Overall conclusions

The overall objective of the present study was to answer four different research questions. This section will recall these questions and the results of the chapters in this thesis, to provide an overall conclusion to the present study.

I. Do VitalSense® capsules inserted deep rectally accurately measure core temperature in anesthetized brown bears (Ursus arctos)?

The DRVS capsules accurately monitored core temperature in comparison to both PA temperature in pigs and gastric temperature in brown bears. This technique also allows frequent and remote monitoring of body temperature, it is easy to perform by a large spectrum of professionals and it is feasible for field captures. One limitation of this technique is the possible occurrence of data loss by the VS monitor, which does not influence the real time monitoring, but might influence the data analysis for research purposes.

II. When compared to both deep rectally and gastrically inserted VitalSense® capsules, do handheld digital thermometers accurately measure core temperature in anesthetized brown bears?

The HDT was not an accurate method of monitoring core temperature in anesthetized brown bears. The bias of this technique, when compared to the gastric temperature, was ± 0.32 °C and 95 % of the readings were underestimating the gastric temperature up to 1.0 °C or overestimating the gastric temperature up to 0.28 °C.
III. Does an active cooling protocol decrease core temperature in hyperthermic anesthetized brown bears?

The active cooling produced a significant decrease in core temperature 10 minutes after the start of the treatment until Time 30 (in comparison to Time 0). However, since some animals still remained hyperthermic, a more efficient and faster way to decrease temperature in hyperthermic bear would be ideal. Continuous administration of cold water enemas might be more efficient.

It is important to emphasize that during an active cooling protocol that includes cold water enemas, the rectal temperature, measured even with an accurate method as the DRVS capsules, is compromised due to the rectal flush of cold water. Thus, rectal temperature does not accurately reflects core temperature during active cooling with cold water enemas in anesthetized hyperthermic brown bears.

IV. Does alpha-2 antagonism decrease core temperature in brown bears recovering from anesthesia?

Atipamezole produced a significant decrease in temperature from 5 to 30 minutes after its administration and it produced an overall decrease in deep rectal temperature that had a tendency to be lower than in the control group. However, it was not possible to conclude if alpha-2 antagonism is an efficient treatment to capture-related hyperthermia in brown bears, since none of the animals in Group A had a core temperature ≥ 40 °C. Nevertheless, evidence found in one hyperthermic bear suggests that the alpha-2 antagonism normalizes thermoregulation instead of decreasing the absolute temperature was found in the present study.
5.2 Limitations

One limitation of this present study was that, due to animal use protocol restrictions, the GVS capsules were only tested in bears captured within the SBBP. This limitation could have affected the final results of the experiments regarding difference of individuals between the populations of brown bears from Scandinavia and from Canada. In addition, due to logistic limitations it was only possible to evaluate the temperature after administration of atipamezole of bears captured within FGBP, and none of them developed hyperthermia. Furthermore, it was not possible to evaluate the techniques of monitoring core temperature and treating hyperthermia in yearlings, since their small size did not allow the use of a stomach tube that would fit the VS capsules inside it. Another limitation was data loss with VitalSense® monitor, which prohibited the use of a more robust statistical approach and decreased the power of the analysis in the present study.

5.3 Overall contributions

The present study contributes to improve the quality of capture of free-ranging brown bears since it indicates the inaccuracy of HDT, a commonly used technique to monitor body temperature in this species. The present study also proposes a novel technique to accurately and continuously monitor core temperature in anesthetized free-ranging brown bears, emphasizing its limitations during the use of cold water enemas for cooling hyperthermic bears and regarding loss of data. I expect that these contributions will impact on decreasing hyperthermia-related morbidity and mortality in free-ranging brown bears.

The most important contributions of the present study were to demonstrate that:
- active cooling protocol significantly decreased core temperature after 10 minutes in anesthetized hyperthermic brown bears;
- atipamezole decreases body temperature of brown bears five minutes after its administration.

However, the present study was not able to evaluate the effectiveness of atipamezole for treatment of capture-related hyperthermia, but data from one hypothermic bear suggests its use may normalize thermoregulation impaired by alpha-2 agonists.

5.4 Future work

Future related work should focus on applying techniques used in the present study for temperature measurement to evaluate alpha-2 antagonist treatment for hyperthermia related to alpha-2 agonists. Further research is needed regarding the accuracy of longer HDTs, temperature after drop following active cooling and the side effects of active cooling. In addition, the techniques of monitoring and treating hyperthermia described in the present study should be adapted and evaluated in yearling bears and other species of wild mammals.
BIBLIOGRAPHY


Health Canada (2012) Drugs and Health Products.


APPENDIX A: EXAMPLE OF AN OUTPUT OF VITALSENSE® DATA FILE.

<table>
<thead>
<tr>
<th>Date/Time</th>
<th>GASTRIC</th>
<th>DEEP RECTAL</th>
<th>Comments</th>
<th>HDT</th>
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<tbody>
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<td>lost packet(s)</td>
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## APPENDIX B: ANESTHETIC MONITORING SHEET

**GRIZZLY BEARS VITALSENSE® PROJECT**

### Drug Protocol

<table>
<thead>
<tr>
<th>Time</th>
<th>Rectal Temp</th>
<th>RR</th>
<th>HR</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
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</tr>
</tbody>
</table>

### Vital Signs

<table>
<thead>
<tr>
<th>Vitals</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>E temp</td>
<td>°C</td>
</tr>
<tr>
<td>RH</td>
<td>%</td>
</tr>
</tbody>
</table>

### General Information

- **Drug Protocol:** ______ (total dose)
- **Date:** ______
- **ID:** ______  **Sex:** ______  **Name:** ______  **Age:** ______
- **Dart Time:** 1st  2nd  3rd
- **BW:** ______ kg

### Additional Details

- **Weather:** ______
- **Distance run before/after dart:** ______
- **Speed before/after dart:** ______
- **Terrain:** ______  **Snow depth:** ______

### Capsule ID

- **Gastric:** ______
- **Rectal:** ______

### Activation Time

- **Insertion Time:** ______

### Medication

- **O₂ time:** ______  **Flow:** ______
- **Nasal line input on snow:** ______
- **1st enema time:** ______
  - **Volume:** ______  **Temp:** ______
- **2nd enema time:** ______
  - **Volume:** ______  **Temp:** ______
- **3rd enema time:** ______
  - **Volume:** ______  **Temp:** ______
- **4th enema time:** ______
  - **Volume:** ______  **Temp:** ______
- **5th enema time:** ______
  - **Volume:** ______  **Temp:** ______

### Drip

- **Start:** ______  **Stop:** ______
- **Fluid:** ______  **Volume:** ______
- **Rate:** ______

### Water/Snow

- **Paws / Groins:** ______
- **Fanning:** Yes / No
- **Shade:** Yes / No
- **How?:** ______

### Reversal Time

- **Dose:** ______

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*Updated by Larissa Mourad Ozeki – April 2012*