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Investigations of the practical application of non-invasive continuous temperature measurement in animal reproduction

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Für meine Familie

TABLE OF CONTENTS

TABLE OF CONTENTS

1 INTRODUCTION

1.1. Introduction

One of the well accepted and core procedures of physical examinations of animals is the measurement of body temperature (Goodwin 1998). Temperature measurement is a simple and safe procedure, which can be easily performed by veterinarians and animal owners (Arlt 2020).

Normal body temperature ranges for different species have been established and nowadays modern and precise devices for the quick measurement are available. Animals with a significant or prolonged elevation of body temperature should be submitted for comprehensive clinical examinations to identify the cause of temperature elevations. However, it has been shown, that the reliability of temperature measurement is dependent of different confounding factors.

Confounding factors may include the used thermometer type (Burfeind et al. 2010), the site of temperature measurement (Chen and White 2006; Gomart et al. 2014) and other aspects such as the depth of insertion depth of the thermometer into the rectum (Burfeind et al. 2010). In addition, the normal temperature ranges may differ during specific conditions (Osinchuk et al. 2014). These conditions can include circadian temperature changes (Refinetti and Piccione 2003), changes related to activity (Panciera et al. 2003) or the temperature of the environment which is for example reflected by temperature variations measured in different months (Suthar et al. 2012a). Other factors may be related to metabolism. In cows the lactation status, usually given as 'days in milk' (DIM) has been identified as a significant influencing factor on average body temperature, presumably because of the high metabolism in cows with high milk yield (Suthar et al. 2012a). In addition, vaccinations and other medical interventions may have an effect on core body temperature, e.g. by effects on the activity of the immune system.

Finally, different phases in the reproductive cycle of mammals may require adjusted temperature ranges (Suthar et al. 2012a). It has been shown that endogenous and exogeneous progesterone affects body temperature in humans (Forman et al. 1987). In cows, it is also believed that progesterone can increase the temperature by 0.3°C, albeit the mechanisms are not fully understood and research findings are contradictory so far (Suthar et al. 2012b). 24 hours after the beginning of aglepristone treatments (progesterone receptor blocker) in dogs, it has been shown that body temperature of pregnant bitches significantly decreased due to abortion and then gradually returned to pre-treatment values (Corrada et al. 2005). However, the authors concluded that body temperature does not seem to be a suitable variable to clinically monitor the aborting effect of the treatment.

Knowledge of these changes is vital in order to interpret temperature findings correctly in the context of potential confounders which may have an effect on normal body temperature ranges. Wrong interpretation of the temperature may lead to false decisions regarding further diagnostic procedures, medical treatment or counseling (Arlt 2020). In many cases, an elevation of body temperature is regarded as an important factor for decisions to use antibiotic treatments or not (Sheldon et al. 2008). In the context of antibiotic stewardship, it can be stated that a correct measurement and interpretation of body temperature is of high relevance and that more research is needed to fully understand confounders and their mechanisms.

1.2 Literature

Body temperature and its regulation in mammals

It is very important for the homoiotherm organism to hold many physiochemical components constant: water content, temperature, gases, pressure and chemical composition (Bernard 1865). Body temperature is maintained constant by the balance between heat production and heat dissipation mechanisms (Tattersall et al. 2016). Thermoregulation involves thermoreceptors and effectors in skin, muscles, mucosa and spinal cord, and the regulation centre in the hypothalamus (Romanovsky 2018). Fluctuation in body temperature can result from changes in set-point value, changes in activity or changes in thermal conductance (Tattersall et al. 2016). Independent thermoeffector loops, receptors and effectors are connected by neural pathways (Romanovsky 2018). One example for a temperature response is the complex physiological reaction to disease involving a cytokine-mediated rise in body core temperature, synthesis of acute-phase reactants, and activation of numerous physiological, endocrinologic, and immunologic systems (Mackowiak 1997).

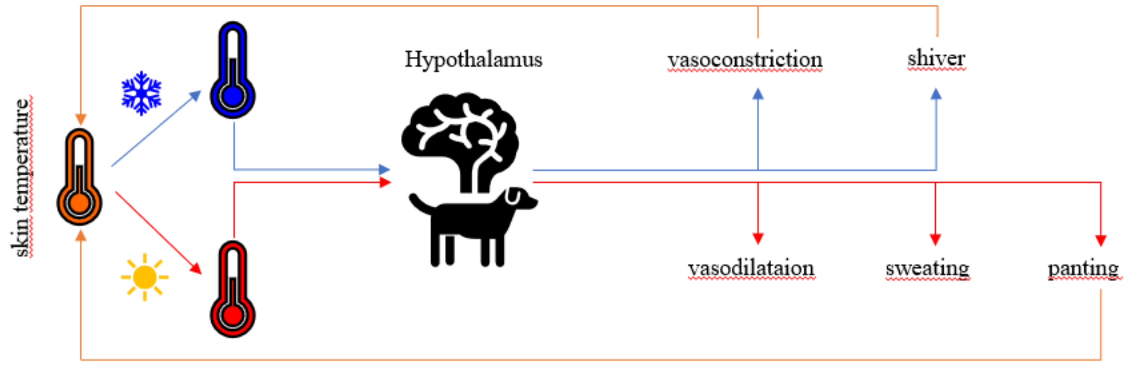

Figure 1: Thermoregulation. Modified from Moyes and Schulte, 2008

Fever

Fever (synonym: pyrexia) has been defined as a significant elevation of body temperature above the species-specific normal range caused by an increase in the individual‘s temperature set point (Dinarello et Porat 2018). It can be hypothesised that such an increase of temperature set-point is a response to various medical conditions and is initiated by physiological and neuronal mechanisms. From a physiological point of view, it warrants a survival benefit for the body during infection (Evans et al. 2015).

Fever is a defensive response of multicellular organisms to the invasion of live or inanimate agents recognized as pathogenic (Mackowiak 2000). Hence, the fever response is in most cases a sign of infection and inflammatory disease which has been shaped through hundreds of millions of years of evolution (Evans et al. 2015). Substances that induce fever are called pyrogens and include toxins or products of viral or bacterial metabolism (Avner 2009).

A significant elevation of body temperature above the species-specific normal range may also be partly or completely based on other factors. For example, during lactation dairy cows may suffer from so called heat stress which is caused by high ambient temperature and an internal heat production caused by an elevated metabolism in phases of high milk yield (Hahn 1999; Kadzere et al. 2002; Mader et al. 2006). In dogs, a progressive increase of temperature from pre-exercise to post-exercise has been described (Angle and Gilette 2011). The rectal measured body temperatures may rise above upper thresholds of temperature references during exercising search and rescue tasks or during dog races (Rovira et al. 2008).

The same phenomenon has been shown in intensively working retrieving dogs (Matwichuk et al. 1999).

Activation of physiologic, endocrinologic, and immunologic systems, cytokines and acute-phase reactants are part of the febrile response (Mackowiak et al. 1997). These factors lead to an increase of the internal temperature set-point (Romanovsky 2018). A restricted range of the upper physiological temperatures supports the activation of resting lymphocytes for proliferation and effector formation in the two major components of the immune system, cell-mediated immunity and humoral immunity (Hanson 1997). Fever can support the immune system's attempt to gain advantage over infectious agents, such as viruses and bacteria, and it makes the body less favorable as a host for replicating viruses and bacteria, which are temperature sensitive (Nalin 2005).

Fever also leads to increases in sympathetic tone, oxygen consumption, respiratory minute volume, and respiratory quotient. In the clinical context, it is important to take into account that individuals with cardiovascular or pulmonary disorders might react more sensible to these effects of fever (Mackowiak 2000).

To control that a temperature elevation does not exceed the range that a body can cope with, biochemical negative feed-back loops become active at high temperatures which protect tissues against damage from overheating caused by excessive cytokine release following infection (Evans et al. 2015). Rising temperature during fever has to be distinguished from the unregulated rise that occurs during hyperthermia, in which pyrogenic cytokines are not directly involved (Mackowiak 2000).

Measurement of body temperature – which methods can be used?

To determine body temperature, Sanctorius, an Italian physician, was the first who used innovative instruments in the early 17th century (Wunderlich and Reeve 1869). In 1851, Wunderlich introduced the first mercurial axillary thermometer and defined the normal body temperature range for humans (Sund-Levander et al. 2002).

In veterinary practices, body temperature is usually measured by rectal thermometry (Fischer-Tenhagen and Arlt 2020). For research purposes, this measurement technique also has been widely used (Berman et al. 1985; Hauptman et al. 1997; Goodwin 1998). For the measurement of rectal body temperature, the measuring probes of analogue or digital thermometers are inserted into the animal’s rectum (Fischer-Tenhagen and Arlt 2020). The temperature can usually be read after a few seconds or minutes.

As alternatives, also auricular and axillary measurements have been tested with moderate to good results (Gomart et al. 2014). However, these techniques are not widely used in veterinary practices. Reasons might include that these techniques seem more prone to distorting factors. Gomart et al. (2014) found gender and coat length to have significant influences on the measurement results. Auricular temperature shows high biases and limits of agreement with rectal temperature so that and interchangeably interpretation of both temperatures is unacceptable for clinical purposes (Sousa et al. 2011). Instrumentation refinement and development, as well as morphologic differences, play an important role in the potential correlation between the rectal temperature and these other locations (Kahng and Brundage 2019).

In research contexts, more invasive but potentially more accurate temperature measurement methods include intraarterial thermodilution output catheters (Haskins et al. 2005), and telemetric microchip transponders (Greer et al. 2007; Kendall et al. 2008; Maeder et al. 2012). Furthermore, sensors implanted into the abdominal cavity (Miyazaki et al. 2002; Refinetti and Piccione 2005; Brown-Brandl et al. 2005), subcutaneously or intravaginal implanted radiotransmitters (Marvin and Reese 1986; Clapper et al. 1990; Kyle et al. 1998) thermistors implanted into the udder (Bitman et al. 1984; Lefcourt et al. 1999), radiotransmitters residing in the reticulum (Bewley et al. 2008) or rumen (Ipema et al. 2008) of ruminants, and ingestible telemetric sensors (Angle and Gillette 2011; Hynd et al. 2014; Osinchuk et al. 2014) have been used in different species.

Body temperature can be measured by continuous and non-continuous measurement procedures. Rectal thermometry is considered to be the standard type of non-continuous measurement of body temperature and the most common method for obtaining body temperature in animals in general (Goodwin 1998). This technique provides temperature data just in time but measurement has to be repeated if temperature patterns or changes are of interest.

For research purposes, continuous measurement techniques may be advantageous (Greer et al. 2007; Quimby et al. 2009) because they may reduce the potential bias of temperatures caused by stress following approaching and handling of the animal during measurement (Greer et al. 2007). Chapon et al. (2011) stated that monitoring unstressed animals is a necessary condition to guarantee reliable and unaffected measurement data. Angle and Gilette (2011) found continuous monitoring of core body temperature to be valuable because it reflects transient and dynamic changes that may not be identified by using non-continuous monitoring.

For continuous temperature measurement in veterinary research, invasive methods have been applied in the past in the majority of projects. Because of ethical concerns, in the future non-invasive techniques should be used whenever possible to improve animal welfare (Chen and White 2006). New technical devices nowadays allow to avoid invasive methods.

Several projects with non-invasive measurement devices used in animals have been published in recent years: The first published vaginal measurement of core body temperature in cattle was performed by Clapper et al. (1990). According to the authors, a much lower degree of invasiveness associated with the measurement procedure could be reached with this technique. In 2010, Vickers et al. published a validation study on vaginal temperature measurement with microprocessor-controlled data loggers in dairy cows.

Since the beginning of the 90th, ingestible temperature sensors have been used for temperature measurements, first in humans and monkeys. In 2011, Angle and Gilette were the first ones who published a study on temperature measurement in dogs with ingestible temperature loggers collecting continuous data in 25 exercising Labrador Retrievers. Nowadays, the use of ingestible telemetric temperature capsules offers accurate and non-invasive measurements of core body temperature in human medicine (Bongers et al. 2018).

In the study of Osinchuk et al. (2014), the comparative analysis of core and rectal temperatures in exercising dogs showed that core temperature rose and declined faster than rectal temperature, and that the core temperatures measured in exercising dogs (range: 39.0°C to 42.5°C, median 40.5°C) were higher than maximum rectal temperatures.

Study	Logger	Animals	Telemetry	Size
Boillat et al. (2010a and 2010b)	MotiliGI: SmartPill Corp, Buffalo, NY	31/6 dogs Mixed-breeds ≥19,6kg	yes	13 x 26mm
Angle and Gilette (2011)	COR-100: Human Technologies, St. Petersburg, Florida, USA	25 dogs Labradors 22.18kg ± 1.41	yes	23 x 10.25mm
Osinchuck et al. (2014)	COR-100: Human Technologies, St. Petersburg, Florida, USA	6 dogs Labradors 20.0kg to 34.8kg	yes	9 x 22mm
Hynd et al. (2014)	Star-Oddi DST Micro-T: Star:Oddi, Gardabaer, Iceland	15 dogs 9 Greyhounds: 28.5kg ± 0.70 6 Labradors: 29.9kg ± 0.56	no	8.3 x 25.4mm

Table 1: Literature on ingestible temperature measurement in dogs

In the past, also temperature measurement techniques have been tested which turned out to be not reliable. For example, a study in which the temperature of 300 dogs was measured using a noncontact infrared thermometer on the cornea compared with a rectal digital thermometer (Kreissl and Neiger 2015). The investigators found that the temperatures correlated poorly as the noncontact infrared thermometer tended to underrecognize hypothermic and hyperthermic conditions in the dogs. The authors concluded that the infrared device cannot be recommended, even if it yields faster results and was significantly more comfortable for the dogs.

Clinical interpretation of body temperature

Convincing evidence is available that body temperature is a useful and sensitive parameter to study the reactions of animals to physiological functions (e.g., nutrition, lactation, and reproduction), environmental challenges, and disease processes (Nakamura et al. 1983). Information about physiological body temperature ranges in different mammalian species seems to be well established. It can be assumed that this is true for many conditions but does not include specific situations such as the puerperium (Arlt 2020).

Species	**Normal temperature range (°C)**
Horse	37.5-38.0
Cattle	38.3-38.8
Sheep	38.5-39.5
Dog	38.0-39.0
Cat	38.0-39.3
Rabbit	38.0-39.5
Rat	37.5-39.5

Table 2: Overview of normal temperature of different species measured in the rectum. Modified from Baumgartner, 2009

Body temperature can be defined as normotherm (body temperature within physiological ranges), hypotherm (body temperature lower than physiological ranges) or hypertherm (body temperature above physiological ranges). Hypothermy can be a result of metabolism failure or insufficient heat transport (for example in cases of circulatory collapse or insufficient blood perfusion in a limb) or low ambient temperatures for a long time (Baumgartner 2009). Body temperature above upper thresholds can be hyperthermy or fever. During fever, rising core body temperature is to be distinguished from the unregulated rise that occurs during hyperthermia, in which pyrogenic cytokines are not directly involved (Mackowiak 2000). Hyperthermia is a result of insufficient thermoregulation when the body is exposed to high ambient temperature or produces more heat by metabolism or muscle action than it can dissipate (Sharma 2007). As stated above, fever is associated with an infectious illness in most cases (Avner 2009).

Body temperature data are always a snapshot in a biological system which is subordinated by fast changes in set-point, changes in activity and changes in thermal conductance (Tattersall et al. 2016). It is important to examine further clinical parameters in addition to body temperature to reach a well-grounded diagnosis which leads to good therapeutical decisions (Sannmann et al. 2013). As an example, with the combination of pathological vaginal discharge and fever as parameters for ante partum metritis (APM), Sannmann et al. (2013) could reduce antibiotic APM treatment by 36.8% and 21.8% in cows with fever in two different treatment groups.

1.3 Objectives

With the scope of continuous measurement with a low degree of invasiveness, we investigated body temperature measurement exemplarily in two different animal species (cows and dogs) and two different research questions in the field of animal reproduction (vaccination/side effects in dairy cows and temperature after parturition in bitches).

A typical side effect of vaccination is an elevation of body temperature often referred to as fever. Research on side effects of vaccinations is essential to understand the effects on the animal�What health and welfare. In addition, such research is required for marketing authorisation and further confirmatory safety trials. Therefore, the objective of the first study was to investigate body temperature changes after vaccination against Q-fever in connection to the parameter milk yield of dairy cows. Q fever is a zoonotic disease caused by *Coxiella burnetii*. The pathogen is prevalent in ruminants (goats, sheep, cows), which are the main sources of human infection. In the cattle industry around the world, animal (15 to 20%) and herd (38 to 72%) level prevalences of *C. burnetii* are high. Vaccination of ruminants against Q fever is considered important to prevent spreading of the disease and risk of infection in humans.

In terms of reproduction management in dog breeding, temperature measurement is an often utilised tool to monitor bitches health in oestrus, early metoestrus and around parturition. Monitoring body temperature in bitches in order to improve prediction of parturition and to enable an early detection of potential dystocia is advised for practitioners and owners (Kim et al. 2007). But, Geiser et al. found in 2014 that although bitches may exhibit a decrease in vaginal temperature around the time of parturition, detecting this decrease does not determine the onset of whelping precisely. They used continuous vaginal measurement of body temperature but without real-time pick up of temperature data. The objective of our second study was to monitor body temperature of post partum bitches with a technique which causes minimal stress and confinement for them and to identify the physiological ranges of body temperature of bitches in the first 7 days after parturition isolated and in connection of leucocyte concentration in the peripheral blood. In a second approach, we analysed the temperature data of the post partum bitches in respect of parallel measuring loggers.

2 RESEARCH PAPERS

2.1 Effect of a phase I *Coxiella burnetii* inactivated vaccine on body temperature and milk yield in dairy cows

2.2 Body temperature of bitches in the first week after parturition measured by ingestible loggers

2.1 Effect of a phase I *Coxiella burnetii* inactivated vaccine on body temperature and milk yield in dairy cows

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2.2 Body temperature of bitches in the first week after parturition measured by ingestible loggers

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3 ADDITIONAL UNPUBLISHED DATA

Parallel measurements of body temperature in bitches in the first week after parturition measured by ingestible loggers

According to the study protocol of the first study “Body temperature of bitches in the first week after parturition measured by ingestible loggers” temperature loggers were administered orally every day. This regimen was chosen to ensure a continuous data measurement because we expected a logger expulsion within 36 hours. In the study of Osinchuk et al. (2014), the mean passage time of ingestible loggers was 1.5 days.

With a maximum passage time of 6 days and 23 hr, some loggers stayed much longer in the dogs’ gastrointestinal tract than expected. Hence, parallel measurements of temperature were recorded in the majority of the dogs (18/20). This opened the question if the data measured by two loggers show a good correlation. Statistical analyses were performed with IBM SPSS Statistics for Windows software (version 24.0; IBM Deutschland GmbH, Ehningen, Germany).

The loggers did not measure the temperature at the exact same time points. Therefore, for the statistical analysis I paired temperature data within a time difference of ≤ 59 seconds. By this procedure, 1609 pairs of temperature data could be determined.

Overall, the difference of measured temperatures was 0.165ºC ± 0.21 (mean ± SD) (figure 1). Minimum differences were 0.0°C, maximum was 2.6ºC. In 81.5% of paired temperature data, the differences were below or equal to 0.2ºC. In 2.7%, the temperature differences exceeded 0.6ºC.

In a second approach, temperatures were paired when they were measured within a period of ≤ 15 seconds. The evaluation of the resulting temperature pairs (n = 401) led to similar data: mean temperature difference was 0.162ºC ± 0.19 (mean ±SD). In 81.0% the temperature difference of paired loggers was below or equal to 0.2ºC.

Figure 1.

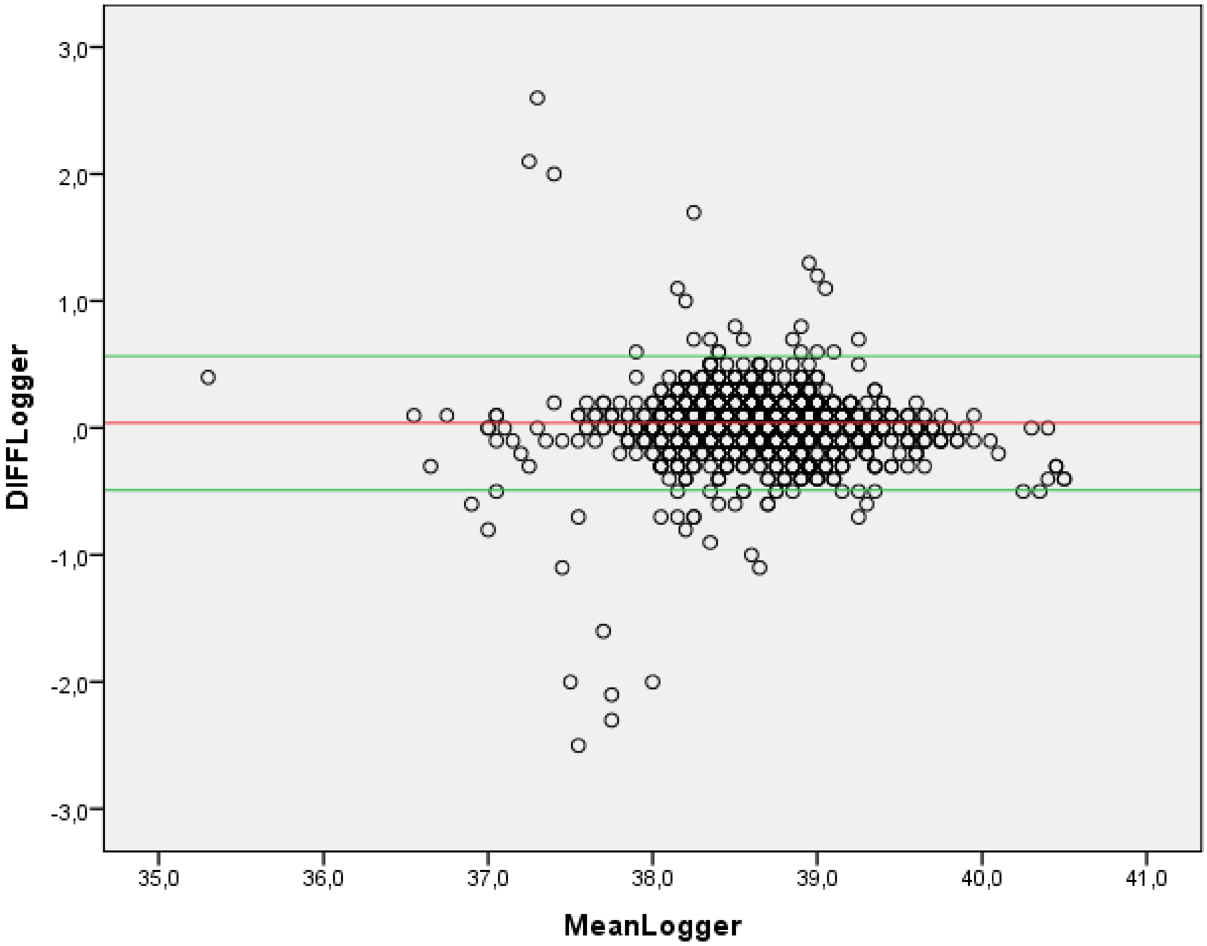

Figure 2. Bland-Altmann-Plot of temperature data (n = 1609) measured by parallel measuring loggers. Pairs of same DIFFLogger:MeanLogger value are shown as one measuring point.

4 DISCUSSION

Impact of body temperature measurement

Body temperature is a useful and sensitive parameter to study the reactions of animals to physiological functions, environmental challenges and disease processes (Nakamura et al. 1983). Temperature measurement has even been described as one of the foundations of physical examination of an animal in clinical veterinary medicine (Goodwin 1998). Therefore, it is regarded to be an essential part of clinical examination that provides valuable information about the actual health status of the patient. Among the physiological parameters, body temperature and its fluctuations are key indicators of health and well-being in animals (Godyn et al. 2019).

Continuous measurement of body temperature

Continuous temperature measurement reduces the potential bias of stress, for example due to handling the animal, on physiological parameters like body temperature. The data presented in the two papers which are parts of this dissertation suggest that through high frequency measurements, the temperature profile can be detected more accurately compared with repeated rectal measurements. The risk to miss peak temperatures and also the risk to overestimate peak temperatures are reduced because temperature can be recorded in short time intervals and also during night times without disturbing the animals.

Scott et al. (1998) suggested that in studies on vaccination and body temperature a 24-h sampling interval from treatment administration until first post treatment measurement may be too long to detect pyrexic changes. In my first study, cows developed fever 11.1h ± 2.6 (mean ± SD) after vaccination. The temperature of febrile cows remained elevated for 3.0 to 46.8h. With a measurement frequency of once a day, only three out of 7 febrile cows would have been detected by rectal measurement. These findings clearly support the recommendations by Scott et al. (1998).

Invasiveness of body temperature measuring methods

The overall objective of this thesis was to assess the clinical usability of temperature loggers in the field of animal reproduction. In that regard, I also wanted to investigate possibilities to reduce invasiveness of continuous temperature measurement.

For cattle, with the development of new technologies for temperature measurement different methods and locations have been researched: on one hand measurement of body surface temperature wire infrared (video) camera, thermal imaging scanner, button-shaped digital thermo-logger and automatic thermistor sensor and on the other hand measurement of deep body temperature in the vagina wire radio transmitter or data logger, in the ear canal wire thermistor, tympanic infrared thermometer or data logger, in the rumen wire rumen bolus and in the rectum wire digital and mercury-in-glass thermometer, data logger, rectal probe or Self-contained indwelling rectal temperature monitoring device (Godyn et al. 2019).

Non-invasive techniques and those that are rapidly accomplished for obtaining temperatures could contribute to improving the animals' welfare in studies (Chen and White 2006). In 2019, Godyn et al. stated that automation of the measurement of the physiological and behavioural parameters of livestock has become an important goal for both scientists and farmers.

To measure continuous core body temperature in cattle, different tools and locations have been used. Some of them, however, were invasive and not always practical and reliable in research settings (Burdick et al. 2012): thermistors implanted in the udder (Bitman et al. 1984; Lefcourt et al. 1999) and radiotransmitters residing in the reticulum (Bewley et al. 2008) or rumen (Ipema et al. 2008). Temperature measurement in the gastro intestinal tract in cattle poeses a challenge because of the anatomic specifics.

A much lower degree of invasiveness of continuous core body temperature measurement can be achieved with tympanic temperature measurement and vaginal temperature measurement in dairy cows. Tympanic temperature measurement by measurement devices placed into an ear in cattle has been described by several authors (Prendiville et al. 2002; Davis et al. 2003; Mader et al. 2010; Godyn et al. 2019). Bergen and Kennedy (2000) write that although the tympanic membrane is situated very close to the hypothalamus, it is difficult to measure tympanic temperature continuously for more than several days because of dislocation of the thermistor and the potential for infection. Acceptance of the tympanic temperature measurement by cows was described different:

Presence of a foreign object in the ear canal may be bothersome (Wiersma and Stott 1983; Bergen and Kennedy 2000). And in the study of Guidry and McDowell in 1965 cows showed no apparent discomfort for 8 or more hours once the probe was in place.

Vaginal measurement of core body temperature in cattle was first described in 1990 by Clapper et al. In 2010, Vickers et al. first validated vaginal temperature measurement with microprocessor-controlled data loggers in dairy cows. Vaginal temperature measurement with a logger attached to a blank controlled internal drug release device (CIDR) is considered being well tolerated by dairy cows in general. Insertion of the device is simple and quick and does not require surgery as do other implantable temperature loggers (Brown-Brandl et al. 2005; Burdick et al. 2012). This approach causes little to no damage posed to tissue in the vagina (Reuter et al. 2010; Burdick et al. 2012). But Ahmadi et al. (2007) observed changes in percentage of neutrophils after CIDR application in dairy cows. CIDR application is common in reproduction management in dairy cows, for example in different reproduction cycle synchronization protocols. After literature research on studies using vaginal temperature measurement in cows, it became apparent that further research is needed about the potential bias on body temperature triggered by changes in the cellular reactions of vaginal tissue. As a consequence, we examined all cows during the first study on inflammation of vaginal tissue. No inflammation signs were found.

For the first presented study, vaginal application of temperature loggers (DST micro-T, Star:Oddi, Gardabaer, Iceland) were chosen because they enable measurement of heart rate and temperature recording. Loggers with the same housing were used for previous studies with vaginal temperature measurement (Maeder et al. 2012). Vaginal temperature measurement wire a blank CIDR in cows was validated by Burdick et al. (2012) with a similar Star:Oddi logger, too.

Research on side effects of vaccinations is essential to understand the effects on the animal's health and welfare. In addition, such research is required for marketing authorisation and further confirmatory safety trials. A typical side effect of vaccination is an elevation of body temperature often referred to as fever.

For the second study, a different method of continuous temperature measurement was selected. Basic consideration behind this was that changes of the milieu in the bitches' vagina may lead to logger loss or unreliable measurements. Previous studies showed that in dogs with little vaginal discharge prior to parturition logger loss occurs although loggers were attached to a silicone blank CIDR device (Geiser et al. 2014). It can be expected that the proportion of losses may be considerably higher in dogs in the first days post partum because of softening of the vaginal tissue and vaginal discharge.

A search in literature revealed that also for temperature measurements in dogs different methods have been used. In dogs, non-continuous auricular temperature measurement is used frequently in research wire infrared thermometry. But instrumentation for continuous tympanic temperature measurement like in the study of Leonov et al. (1990) has only been applied and maintained under anesthesia. In the light of new technical devices general anesthesia seems not to be ethical to enable continuous temperature measurement anymore.

The use of ingestible telemetric temperature capsules offers an accurate and non-invasive measurement of core body temperature in human medicine (Bongers et al. 2018). In 2011, Angle and Gilette were the first who published a study on temperature measurement in dogs with ingestible temperature loggers collecting valuable continuous date. They stated that telemetric core temperature monitors may offer an easier and more comfortable means of sampling core temperature with minimal human and mechanical interference with the exercising dog. According to the study of Hynd et al. (2014), the used ingestible temperature loggers provided data likely to be more accurate than rectal, aural or skin surface measurements.

Because of the composition of our clinic's client dogs, our probands had lower body weight than the dogs in the five studies presented in table 2, which discloses studies using ingestible temperature measurement in dogs. BodyCap (Caen, France) produces a wireless temperature logger (Anipill) which was licensed for the ingestible use in general (BodyCap, Anipill System User Guide, 2015). The size of the Anipill capsules we used is smaller than the loggers used in the cited studies: 17.7 × 8.9 mm. In a study with ducklings, good application security and bio compatibility of Anipill was found (Tattersall et al. 2016). Hence, we decided to use the Anipill for long term core temperature measurement in post partum dogs.

In dogs, the first days after parturition are characterized by many claims raised by nursing the puppies, uterine involution, milk production and hormonal changes (Arlt 2020). Hence, in this period bitches are supposed to be more susceptible to pathologic conditions. Therefore, it is important to monitor vital functions, appetite and behaviour of post partum bitches on a daily basis to enable early detection of illness (Grundy and Davidson 2004). We measured long term core temperature in post partum bitches. The physiological ranges of body temperature of healthy bitches in the first days after parturition did not differ from those of healthy dogs in general, while the appearance of short episodes of febrile temperatures seems to be physiological. Temperature measurement is, however, an important diagnostic tool for health surveillance of bitches after parturition. A continuous measurement of the bitches' body temperature could improve early detection and treatment of potential puerperal disorders in time. Therefore, continuous temperature measurement in the bitch could support the bitch, the puppies and future fertility.

New technologies may allow safe and reliable monitoring of body temperature in practice or even at home. This will allow a good health surveillance of dogs at higher risk of diseases such as situations prior to or in the first days after parturition.

Also, new technology may allow health monitoring in cattle. Loggers that will be able to collect measurements of different parameters such as temperature, heart rate (Warren et al. 2008), pH and others are under development or already on the marked that may add further information in the future.

Parallel measurements of body temperature in different gastrointestinal locations

Statistical analyses of the temperature data of parallel measuring loggers showed temperature differences of 0.165ºC ± 0.21 (mean ± SD). In 81.5% of the cases, temperature differences were lower or equal to 0.2ºC.

It can be assumed that the loggers measured slightly different temperatures in the different parts of the gastrointestinal tract. According to the manual the logger's producer guarantees an accuracy of ± 0.1-0.2°C (BodyCap, Anipill System User Guide 2015). In a preliminary validation of all used loggers, we compared measurement results with a calibrated liquid-in-glass thermometer in a water bath and the mean difference was ± 0.1°C. These differences can be considered being acceptable, also under clinical circumstances.

Osinchuk et al. (2014) administered CorTemp® sensors orally to fasted Labrador retriever dogs and took radiographs to document the exact sensor locations. They found smaller differences between core temperature and rectal temperature when the sensor was in the transverse colon (difference 0.31ºC) compared with greater differences between core temperature and rectal temperature when the sensor was located in the descending colon (difference 0.56ºC). However, temperature differences based on different gastrointestinal locations were not significant (Osinchuk et al. 2014).

In the presented study, temperature data was excluded from the analysis if it was below 35.1°C because we assumed that lower temperature corresponded with loggers being outside the canine body. I did not exclude data from loggers that were supposedly located and measuring temperature in the stomach or cranial duodenum. It can be assumed that some measurements may have been influenced by drinking cold water or food intake.

Body temperature data is always a snap-shot in a biological system which is subordinated by fast changes in set-point, changes in activity and changes in thermal conductance (Tattersall et al. 2016). A smaller time frame to define paired temperature data (reduction from maximum time delay of 59 sec to ≤ 15 sec) led to no better accordance (0.165ºC ± 0.21 (mean ± SD) vs. 0.162ºC ± 0.19 (mean ± SD)).

From a clinical perspective, most measurements did not differ more than 0.2°C which can be considered tolerable. It still can be assumed that temperature measured by ingestible loggers might be of better reliability than a measurement in the rectum. In case of elevated temperatures or temperatures below the threshold, I suggest another measurement within five to 10 minutes and in addition also after longer time intervals. Ideally clinical decisions should be based on multiple temperature measurements.

5 SUMMARY

Non-invasive continuous temperature measurement in animal reproduction

Continuous measurement of body temperature provides an extensive insight into the complex variations of body temperature within the given range of physiological and pathological temperature of animals. To reach the aims of investigations with a low degree of invasiveness, is an important objective in modern science. Within this scope, we investigated body temperature measurement exemplarily in two different animal species and two different research questions in the field of animal reproduction.

In the first study, body temperature was measured by rectal measurement and vaginally under the terms of a study on the effect of the phase I *Coxiella burnetii* inactivated vaccine Coxevac on body temperature and milk yield in dairy cows. Q fever is a zoonotic disease caused by *C. burnetii*. The pathogen is prevalent in ruminants (goats, sheep and cows), which are the main sources of human infection. In the cattle industry around the world, animal and herd level prevalences of *C. burnetii* are high. Vaccination of ruminants against Q fever is considered important to prevent spreading of the disease and risk of infection in humans. However, published information on side effects of the Q fever vaccination under field conditions is limited for cows. In two experiments, a total of 508 cows were randomly divided into two groups to determine the effect of first vaccination on body temperature and milk yield. The first experiment took place in the teaching and research barn of the Clinic of Animal Reproduction at the Freie Universität Berlin. Temperature of 10 cows was measured vaginally with temperature data loggers housed in modified controlled internal drug release devices without progesterone (CIDR) in a crossover design. The second experiment was conducted on a commercial dairy farm. Milk yield of 498 cows was measured one week before and one week after vaccination. In a subset of 41 cows, temperature was measured rectally with digital thermometers. Body temperature increased significantly after vaccination and a significant difference was also found in body temperature between vaccinated and control cows. Thirty percent of the vaccinated animals in experiment 1 showed reversible swelling at the injection site as a reaction to the vaccination. The results indicate that vaccination against Q fever causes a transient increase of body temperature that peaks in the first 12 to 24 hours and declines after that. In experiment 2, vaccinated cows produced significantly less milk than did control cows 7 days after first vaccination. The cumulative milk loss after first vaccination was influenced by an interaction between *C. burnetii* serostatus and average milk yield 7 days before first vaccination. This was considered as part of the physiological immune response.

In the second study, body temperature of bitches in the first 7 days after parturition was measured with ingestible temperature loggers. The first days after parturition in dogs are characterized by many claims raised by nursing the puppies, uterine involution, milk production and hormonal changes. Hence, in this period, bitches are supposed to be more susceptible to pathologic conditions. The study was performed on 20 private-owned bitches of different breeds. The bitches stayed in their common environment. The ingestible temperature loggers were programmed to measure core body temperature every 15 minutes. Seven loggers and a monitor which they were connected with were given to the owners between day 56 of pregnancy and start of parturition. Each bitch swallowed one ingestible temperature logger daily. Bitches were defined to be healthy by spontaneous parturition and leukocyte concentration. Body temperature of healthy puerperal bitches did not differ from those of healthy dogs in general, while the appearance of short episodes of febrile temperatures seems to be physiological. Body temperatures differed significantly between weight classes showing that small bitches had higher temperatures. Puerperal bitches with leucocytosis showed significant higher body temperatures. Animals did not show any signs of distress.

Parallel measurements of temperature were recorded in the majority of the dogs (18/20) involved in the second study. For the statistical analysis, we paired temperature data within a time difference of ≤ 59 seconds (n = 1609) and ≤ 15 seconds time difference (n = 401), respectively. The difference of measured temperatures was 0.165ºC ± 0.21 (mean ± SD) for the maximum 59 seconds pairs and 0.162ºC ± 0.19 (mean ±SD) for the maximum 15 seconds pairs. From a clinical perspective, most measurements did not differ more than 0.2°C which can be considered tolerable. It still can be assumed that temperature measured by ingestible loggers might be of better reliability than a measurement in the rectum. In case of elevated temperatures or temperatures below the threshold, repeated measurements are advised for clinical decisions.

6 ZUSAMMENFASSUNG

Nicht-invasive, kontinuierliche Messung der Körpertemperatur in der Reproduktionsmedizin der Tiere

Die kontinuierliche Messung der Körpertemperatur liefert einen erweiterten Einblick in die komplexen Zusammenhänge der Körpertemperatur innerhalb deren physiologischen und pathologischen Grenzen bei Tieren. Wissenschaftliche Fragestellungen mit einem möglichst niedrigen Grad von Invasivität zu erörtern ist ein wichtiges Ziel der modernen Wissenschaft.

In diesem Kontext führten wir zwei Studien zur Körpertemperatur bei zwei unterschiedlichen Tierarten und mit jeweils unterschiedlicher Fragestellung innerhalb der Tierzucht durch: In der ersten Studie wurden die Körpertemperatur und die Milchleistung während einer Impfstudie am Milchrind untersucht. Als Messmethoden für die Körpertemperatur wurden die rektale Messung mit digitalen Thermometern und die vaginale Messung mit Temperaturloggern in Vaginalspiralen ohne Hormonbeschichtung als Trägersystem gewählt. Gegenstand der Untersuchung waren die möglichen Auswirkungen einer Erstimpfung mit dem inaktivierten Q-Fieber-Impfstoff Coxevac der Firma Ceva Santé Animale. Q-Fieber ist eine Zoonose, ausgelöst durch die Infektion mit dem Bakterium *Coxiella burnetii*. Das Pathogen weist eine starke Prävalenz in Wiederkäuern (Ziegen, Schafen und Kühen) auf. Diese Tiere und ihre Ausscheidungen stellen die Hauptinfektionsquellen für den Menschen dar. Die Q-Fieber-Impfung der Wiederkäuerpopulation ist ein wichtiges Mittel zur Prävention gegen eine Ausbreitung dieser Erkrankung. Das Risiko einer Übertragung auf den Menschen wird durch die Impfung reduziert. Trotz eines weiten Einsatzes von Q-Fieber-Impfstoffen wurden bisher kaum Informationen über mögliche Nebenwirkungen der Impfung für Kühe veröffentlicht.

In unserer ersten Studie wurden in zwei Experimenten insgesamt 508 Kühe in je zwei zufälligen Gruppen auf die möglichen Auswirkungen einer Erstimpfung mit dem inaktivierten Q-Fieber-Impfstoff Coxevac auf Körpertemperatur und Milchleistung hin untersucht. Das erste Experiment fand im Versuchsstall der Fortpflanzungsklinik der Freien Universität Berlin statt. Hier wurden die Körpertemperatur und weitere Nebenwirkungen der Impfung auf die Kühe untersucht. Für das zweite Experiment fand auf einem konventionellen Milchviehbetrieb statt. Die Milchleistung von 498 Kühen wurde in einem Zeitraum von einer Woche vor der Erstimpfung bis einer Woche nach dieser aufgezeichnet. In einer Untergruppe von 41 Tieren wurde die Körpertemperatur durch rektale Messung bestimmt. Die Körpertemperatur der Kühe stieg in beiden Experimenten signifikant nach der Impfung an. Geimpfte Tiere zeigten eine signifikant höhere Körpertemperatur als ungeimpfte Tiere. Im ersten Experiment entwickelten 30% der geimpften Kühe eine reversible Schwellung an der Injektionsstelle als Reaktion auf die Impfung. Die Impfung gegen Q-Fieber durch Coxevac führt zu einem vorrübergehenden Anstieg der Körpertemperatur mit Höchstwerten in den ersten 12 bis 24 Stunden nach der Erstimpfung. Im zweiten Experiment erbrachten die geimpften Kühe signifikant weniger Milchleistung in den ersten sieben Tagen nach der Erstimpfung als die Tiere der Kontrollgruppe. Der kumulative Verlust an Milchleistung wurde beeinflusst vom *C. burnetii*-Serostatus und der durchschnittlichen Milchleistung an den sieben Tagen vor der Erstimpfung. Die veränderte Milchleistung wurde als Teil der physiologischen Immunreaktion auf die Impfung gewertet.

In der zweiten Studie wurde die Körpertemperatur von Hündinnen an den sieben Tagen nach der Geburt ihrer Welpen mit verschluckbaren Temperaturloggern untersucht. Die ersten Tage nach der Geburt ihrer Welpen sind gekennzeichnet durch verschiedenste Ansprüche an die Hündin: das Säugen der Welpen, die Rückbildung der Gebärmutter, die Milchproduktion und hormonelle Veränderungen. Hündinnen reagieren in dieser Zeit deutlich sensibler auf pathologische Stimuli. In dieser Studie untersuchten wir 20 Hündinnen verschiedener Rassen. Die Hündinnen verblieben für die gesamte Studiendauer in ihrem gewöhnlichen Umfeld. Die verschluckbaren Temperaturlogger wurden programmiert alle 15 Minuten die Umgebungstemperatur aufzuzeichnen. Zwischen Trächtigkeitstag 56 und Beginn der Geburt erhielten die Besitzer der Hündinnen sieben Logger und einen mit den Loggern verbundenen Monitor. Jede Hündin schluckte über sieben Tage jeweils einen Logger täglich. Die Definition des Gesundheitsstatus der Hündinnen erfolgte über die Leukozytenkonzentration im peripheren Blut. Es zeigten sich keine Unterschiede in der Körpertemperatur der gesunden Hündinnen in Vergleich zu den Referenzwerten gesunder Hunde im Allgemeinen. Das Auftreten kurzer Episoden mit fiebrig erhöhten Temperaturwerten scheint in den ersten Tagen nach der Geburt bei Hündinnen physiologisch zu sein. Zwischen definierten Gewichtsklassen innerhalb der Studienpopulation konnte ein signifikanter Temperaturunterschied festgestellt werden, wobei kleine Hündinnen höhere Temperaturen zeigten als große. Keines der Tiere zeigte aversives Verhalten oder pathologische Reaktionen auf die Applikation der Logger hin oder deren Verbleib im Körper der Tiere über mehrere Tage.

Achtzehn von 20 Hündinnen wiesen in der Auswertung der Temperaturdaten parallele Messungen unterschiedlicher Logger auf. Für eine statistische Analyse der parallel gemessenen Temperaturwerte bildeten wir zwei Gruppen von Paaren aus Temperaturdaten mit einer Zeitdifferenz der Messungen von weniger als einer Minute (n = 1609) und maximal 15 Sekunden (n = 401). Der mittlere Temperaturunterschied lag in der 59-Sekunden-Gruppe bei 0.165ºC ± 0.21 und in der 15-Sekunden-Gruppe bei 0.162ºC ± 0.19. Aus der klinischen Perspektive heraus sollten Messdifferenzen von 0.2°C für die Körpertemperatur tolerabel sein. Es kann angenommen werden, dass Körpertemperaturwerte, die von verschluckbaren Loggern gemessen wurden, zuverlässiger sind als rektal gemessene Werte. Dennoch sollte bei klinischen Entscheidungen im Fall erhöhter Temperaturwerte oder Werten unterhalb von bekannten Grenzwerten eine Mehrfachmessung vorgenommen werden.

7 REFERENCES FOR INTRODUCTION AND DISCUSSION

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8 PUBLICATIONS

8.1 Research articles

L. S.-Ch. Schulze, S. Borchardt, V. Ouellet, and W. Heuwieser (2016):

Effect of a phase I *Coxiella burnetii* inactivated vaccine on body temperature and milk yield in dairy cows. Journal of Dairy Science. 99 (1): 541-500

http://dx.doi.org/10.3168/jds.2015-9628

L. S.-Ch. Schulze, W. Heuwieser and S. P. Arlt (2018):

Body temperature of bitches in the first week after parturition measured by ingestible loggers. Reproduction in Domestic Animals. 53(Suppl 3): 63-69

http://dx.doi.org/10.1111/rda.13330

8.2 Oral presentations at conferences

L. S-Ch. Schulze, W. Heuwieser and S. P. Arlt (2017):

Do bitches with high leucocytosis after parturition show higher temperatures? A pilot study. 20. EVSSAR Congress - Reproduction and Pediatrics in Dogs, Cats and Small Companion Animals: Wien/Österreich. 20.06. – 01.07.2017

8.3 Poster presentations at conferences

L. S.-Ch. Schulze, W. Heuwieser, and S. P. Arlt (2017):

What is the body temperature measured by ingestible loggers in healthy bitches after parturition? Welche Körpertemperatur – gemessen mittels verschluckbaren Temperaturloggern – ist bei Hündinnen nach der Geburt normal? 50. Jahrestagung Physiologie und Pathologie der Fortpflanzung: München. 15.-17.02.2017. Reproduction in domestic animals; 52 (Suppl 1):48. ISSN: 0936-6768

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10 DECLARATION OF INDEPENDENCE

Hiermit bestätige ich, dass ich die vorliegende Arbeit selbständig angefertigt habe. Ich versichere, dass ich ausschließlich die angegebenen Quellen und Hilfen in Anspruch genommen habe.

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Laura S.-Ch. Schulze