AALBORG UNIVERSITY
MASTER'S THESIS

Testing the effect of a new pleural catheter "HeatCath®" for the treatment of moderate hypothermia in a porcine model

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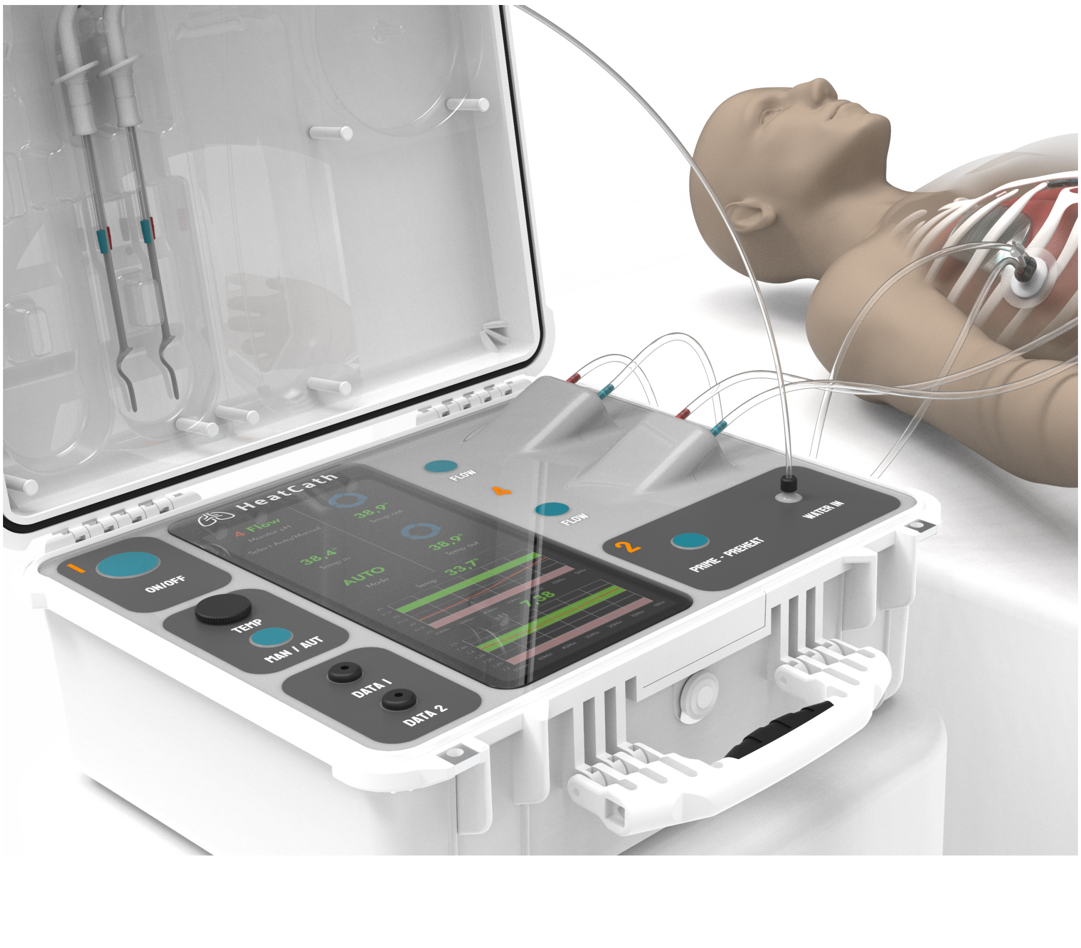


Abstract

Aim of the study: To demonstrate the effect of a new device for treating and supporting patients with moderate accidental hypothermia, tested in a porcine model. Validation of rewarming capabilities is done by comparing the experimental results with data from already known techniques, through a literature review. A target rewarming rate (°C/h) for HeatCath is furthermore to be settled under the criterion that it meets the lowest rewarming rate, defined as 25. percentile, of the best technique used for treating accidental moderate hypothermia.

Methods: Anesthetized pigs (n= 2 weighing 49 -53 kg) were cannulated for ECMO and cooled to 26 °C. Core temperature was measured by a catheter in the bladder and one in the abdomen. Pigs were randomly selected into one of two groups (i) Intervention-group (n=1) rewarmed for 3,5 hours through the insertion of a central warming catheter "HeatCath®". (ii) No treatment was applied to the control group (n= 1). When the intervention pig was warmed for 3,5 hours, the rewarming technique was applied to the control animal for further analysis of practicality and rewarming rates at a given temperature.

Results: Through literature review, it was confirmed that pleural lavage is the best contemporary rewarming technique for moderate hypothermia, and the rewarming rate was equal to 2,8 °C/h, thereby defined as our target rewarming rate for HeatCath. Through the experimental rewarming phase of 195 min, the average rewarming rate was 1,3 °C/h for the intervention versus 0,4 °C/h for the control. During rewarming of the control animal, a mean MAP of 61 mmHg (±7 mmHg) with a heart rate of 57 bpm, and the intervention animal had a mean MAP of 71 mmHg (± 8 mmHg) with a heart rate of 57 bpm (± 13 bpm). Initiating the treatment with HeatCath on the control pig after 195min, showed a rewarming rate on 1,1 °C/h. during a 60 min. period.

Conclusion: HeatCath produced a rewarming rate of 1,3 °C/h in the intervention pig. 0,9 °C/h greater than the non-treated control pig, during the rewarming time of 195 min. Initiating treatment with HeatCath on the control animal after 195 min. at a temperature of 27,1 °C produced a rewarming rate of 1,1 °C/h over 60 min. The display of functionality and controlled rewarming fulfilled the expectations. The intervention animal presented more stable vital signs compared to the control animal, but the aim of a rewarming rate of 2,8 °C/h was not met, and further development of HeatCath could be beneficial.

1 | Introduction

Accidental Hypothermia (AH) is defined as an involuntary decline of body temperature < 35 °C. It is estimated that approximately 100 -200 victims are hospitalized due to hypothermia yearly in Denmark. Furthermore, around 15 have a fatal outcome [1]. It is a relatively rare diagnosis, but the impact of hypothermia is high. Mortality is seen both during hypothermia and after rewarming treatment. Treatment guidelines are often ambiguous and there is a lack of consensus on which rewarming methods to use.

Causes of AH are multiple and can be divided into primary or secondary, whereas primary refers to hypothermia in an otherwise healthy individual, and secondary refers to adjacent hypothermia due to underlying conditions in an already weakened individual. Depending on the severity hypothermia causes a multitude of complications .[2]

The degree of decline in temperature contributes to adverse physiological changes due to the failure of compensatory metabolic, adrenergic, and cardiovascular responses in managing thermal homeostasis. As a result, systemic and organ dysfunction such as coagulopathy, acid-base disorder, cardiac irritability or failure, respiratory failure, as well as neurological dysfunction can occur.[2]

Classification of AH is defined in a wide variety through the literature. Some are based on the clinical presentation of the patient, and some are exclusively based on the core temperature[2] ,[3]. A widely approved method compares clinical factors and body temperature as a guideline to the severity of hypothermia and to help dictate the needed treatment. According to temperature and clinical factors, AH can be divided into three groups: mild, moderate, and severe[4].

Mild: The core temperature is less than 35 °C, but the patient is awake. This patient can be rewarmed by the body's endogenous system when protected from cold exposure, or externally using warm forced air, warm water immersion, hot air inhalation, or warm drinks.[5]

Moderate: Core temperature is less than 32 °C, the patient is unconscious, but heart rhythm seems stable. In this case, the patient may benefits from being intubated and ventilated. An essential central rewarming is most suitable since these patients have impaired endogenous thermic regulation, potential hypotension and a significant risk of atrial fibrillation. Treatment such as warm cavity lavage, hemofiltration, and venous heat catheter is described as being beneficial, but there is no determined ranking of methods in the literature for moderate AH, except the use of extracorporeal circulation (ECC) if an eminent risk of circulatory collapse is present.[4],[6]

Severe: The core temperature is less than 32 °C and the circulation is collapsed. The patient receives CPR until the core temperature is high enough for defibrillation. The safest and most effective rewarming method is ECC and blood warming[7], [8].

The approach to treating mild and severe hypothermia is well-reviewed in the literature, while no golden standard for treating moderate hypothermia is acknowledged. A clinical paper from 2020 shows that the Danish paramilitary retrieval team for accidental hypothermia has treated 56 patients for moderate hypothermia (survival 82 %). These patients were treated with: 38 % pleural lavage, 2 % ECC and 60 % blankets[9]. This indicates that the preferred active rewarming method for moderate hypothermia in the Danish paramilitary is pleural lavage. Pleural lavage utilizes central warming which has some obvious advantages compared to peripheral rewarming. Peripheral rewarming is prone to cause transmission of cold, acidotic blood from the extremities to the core causing temperature and pH to drop. Furthermore, peripheral rewarming tends to increase the metabolism of the peripheral cells in the body, which accelerate cell damage due to the low peripheral blood circulation of the hypothermic patient[6].

Despite pleural lavage's efficacy, it is rarely described in the literature. However, some specifications are revealed e.g. it approximately requires the same amount of saline fluids per liter as the patient's body weight per kg. The pleural cavity can obtain a volume of about half a liter at a time, hence requiring multiple flushes [9]. It has an estimated rewarming rate of 2,5-7,5 °C /h[10].

The limitation of using pleural lavage in moderate AH is the lack of beneficial effects if the patient develops circulatory collapse. Furthermore, case reports have shown that pleural lavage can compromise circulation and reduce the quality of CPR in case of circulatory collapse, as well as the possibility of causing electrolyte shift[7]. The primary reason for not using pleural lavage in a prehospital setting is due to the method's requirement of large volumes of heated water, which furthermore has vast limitations in cold climates where the heat loss of the water can be enormous depending on the surrounding temperature[7].

Every method has its pros and cons and despite limitations and complications, pleural lavage is broadly agreed upon as being very efficient in the treatment of moderate hypothermia, however, it lacks documentation of its efficacy on humans in the literature[8],[5].

1.1 | The invention of a new pleural catheter

During a Danish military exercise in Northeast Greenland in 2015 it seemed obvious that rewarming using pleural lavage was not an option due to the cold climate, primitive settings, and logistical challenges. This initiated the invention of an alternative device called HeatCath©. The device utilizes the same principle of core warming by thoracic access, but in contrast to lavage, it consists of a closed-circuit pleural heating catheter, warmed by water within its circuit.

The aim of this study was to test the rewarming capacity of HeatCath in a porcine model.

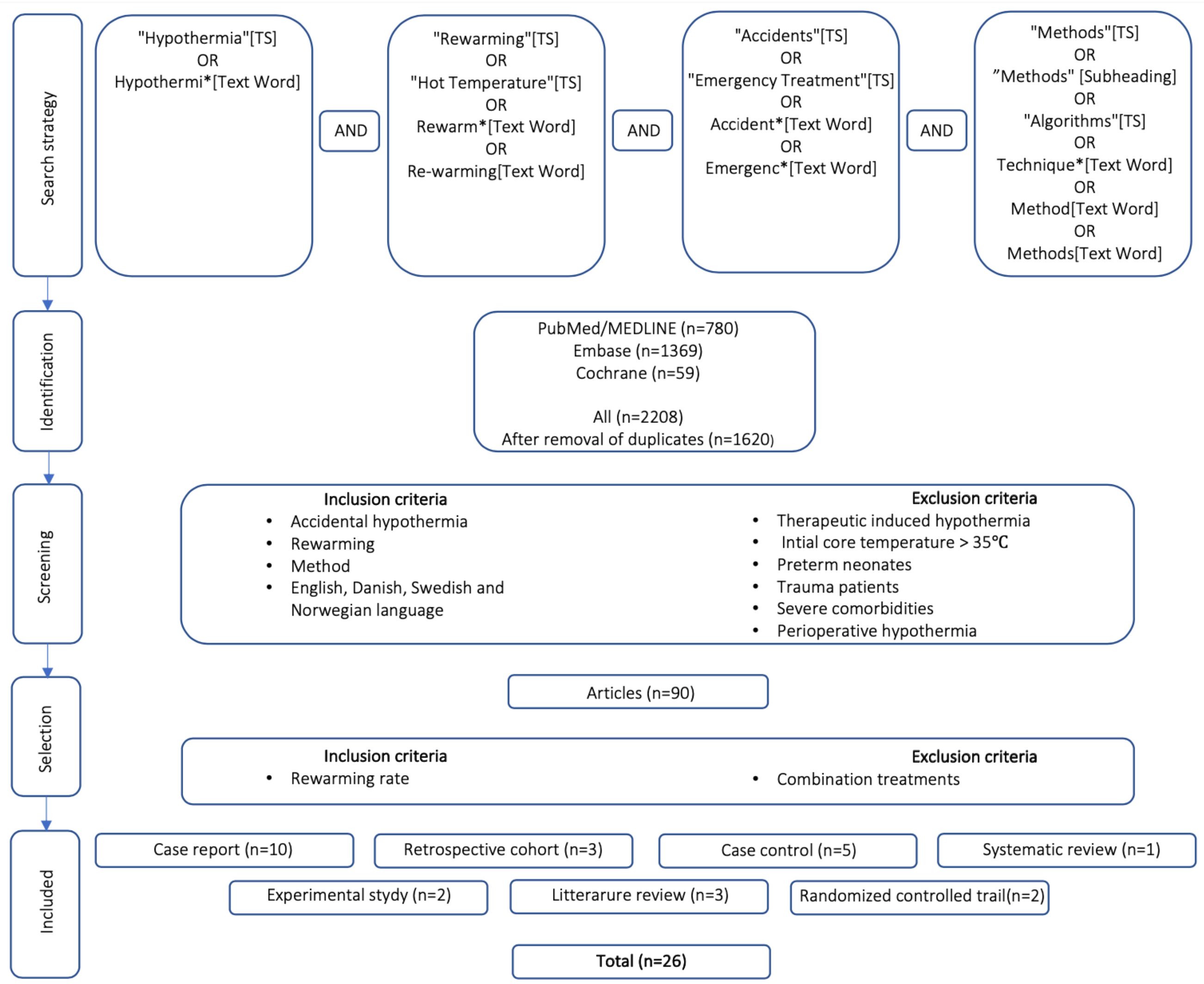
1.2 | Which rewarming methods exist in the literature, and what is the rewarming capacity?

The main purpose of the literature review was to reveal all existing methods used to treat accidental hypothermia prehospital and in-hospital. Furthermore, the effect of each method was to be evaluated according to the rewarming rate stated in the articles.

A literature search of PubMed, MEDLINE, EMBASE, and Cochrane Library, was carried out in October 2022. All article formats were included. Free-text search terms and terminology were used (**Flowchart 1**). An open approach was used regarding the search criteria and the selection of article formats, a necessity to include all relevant articles due to the inconsistent use of terminology throughout the literature. For narrowing down the search a set of essential inclusion and exclusion criteria was inserted.

1.3 | Results of the literature search

After the removal of duplicates, 1620 articles were screened, and 90 met our first search criteria. These articles formed a base of information to cover all existing rewarming methods. To evaluate the effect of each method, another inclusion criterion was added: "rewarming rate". In addition, an exclusion criterion was added "combination treatments" to ensure the true rewarming rate for each.



Flowchart 1: *literature approach showing a simplified search strategy used for all databases. Thesaurus (TS). Identification = the total number of articles found in each database, and the sum of articles after the removal of duplications. Screening = 1620 articles were run through a filter of inclusion and exclusion criteria leaving a sum of 90 relevant articles. Selection = for specifications regarding the effect of each method additional inclusion (rewarming rate) and exclusion (combination treatment) criteria are added. Included = the total number of included articles (26), distributed on various types of articles.*

Articles found after the first screening contributed to conducting a table of all existing rewarming methods contained in the literature as seen in (**Table 1**).

Even though a wide search strategy was used, a low number of articles was describing the rewarming rates with sufficient information to draw a clear conclusion about the eligibility of each method. Many articles had poor scientific quality. It seems like the evidence on this topic is very inhomogeneous.

Information regarding rewarming rate was extracted from the data of each method. As a minimum, the data needed to be represented in more than one case. Nine methods provide enough data for further analysis. Many variables influence the outcome of the rewarming rate e.g the course and severity of AH, biochemical factors, initial temperature, surrounding temperature and respirator settings.

Therefore, an isolated conclusion on the efficacy of rewarming is hard to extract and comparisons between rewarming rates are inconclusive. Despite this inconsistency, a trend is somewhat feasible to extract. (**Figure 1)** showing the span of the rewarming rates (end temperature minus initial temperature divided by duration time). In addition to the rewarming rate, data on the magnitude of afterdrop (further cooling, even after rewarming has started[7].) was collected for all methods. Typically, passive rewarming, like blankets, produces a small but more sustained magnitude of afterdrop ranging from 0,2 °C to 1 °C. Forced air and hot inhalation show a slightly lower magnitude of afterdrop ranging from 0,2 °C to 0,5 °C. No significant afterdrop was reported in the invasive methods [5].

Endogenous rewarming
  - Basal metabolism
  - Shivering
  - Exercise

Exogenous rewarming
- External, passiv
  - Blankets
  - Carbon fiber blanket
  - Foil blanket
- External, active
  - Human body
  - Hot objects (water bottles)
  - Warmed blankets
  - Chemical heating pads
  - Radiant heat
  - Warm water immersion
  - Forced air warming
- Internal, noninvasive
  - Hot drinks
  - Inhalation of heated saturated air
- Internal, invasive
  - Warm iv fluids
  - Lavage (rectal, bladder, gastric, peritoneal, pleural)
  - Endovascular catheter
  - Renal replacement therapy
  - ECC (Venovenous, venoarterial)

Table 1: *Existing methods used in treating hypothermia*

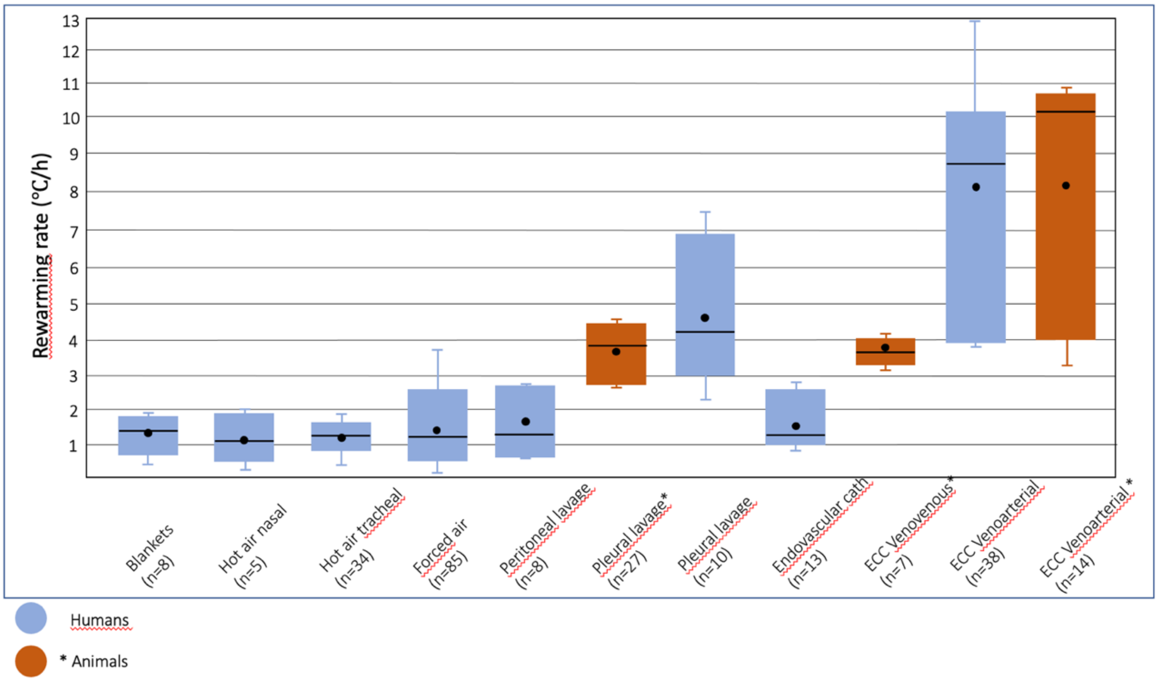


Figure 1: *Showing the span of the rewarming rate, calculated from the data of nine methods. X =representing different rewarming methods. Y =°C/h. For each method, the following values are illustrated: Minimum; maximum; lower percentile (Q1); upper percentile (Q3). The black line marks the median, and the black dot marks the mean. The following results are observed regarding the rewarming rates for the respective methods. Blankets*[3], [11]–[13]*: presented with a; lower percentile = 1 °C/h, Mean =1,3°C/h, upper percentile = 1,7 °C/h. Hot air nasal* [14], [15]*: lower percentile = 0,6 °C/h, Mean=1,1 °C/h, upper percentile = 1,7 °C/h. Hot air tracheal* [16]*: lower percentile = 1,2 °C/h, Mean = 1,2 °C/h, upper percentile = 1,2 °C/h. Forced air* [5], [13], [14]*: lower percentile = 0,9 °C/h, Mean =1,3 °C/h, upper percentile = 1,3 °C/h. Peritoneal lavage* [17]*: lower percentile = 0,8 °C/h, Mean = 1,5 °C/h, upper percentile = 2,5°C/h. Pleural lavage Humans* [18]*: lower percentile = 3,6 °C/h, Mean = 4,7 °C/h, upper percentile = 6,1 °C/h. Pleural lavage animals* [19]–[21]*: lower percentile = 2,8 °C/h, Mean = 3,6 °C/h, upper percentile = 4,1 °C/h. Endovascular catheter* [22]*: lower percentile = 1,1 °C/h, Mean = 1,1 °C/h, upper percentile = 1,1°C/h. ECC venovenous animals* [23]*: lower percentile = 3,5 °C/h, Mean = 3,7 °C/h, upper percentile = 3,9 °C/h. ECC venoaterial humans* [24]*: lower percentile = 8,8 °C/h, Mean = 8,1 °C/h, upper percentile = 8,8 °C/h. ECC venoarterial animals* [23], [25]*: lower percentile = 4,5 °C/h,Mean = 8 °C/h, upper percentile = 10,8 °C/h.*

1.4 | Comparing the different rewarming methods

Comparing the non-invasive methods (blankets, hot air inhalation, and forced air). The rewarming rates tend to be similar according to the boxplot showing the lowest mean rate of 1,1 C°/h for hot air nasal and the highest mean rate of 1,3 C°/h for blankets and forced air. Unexpectedly active rewarming such as forced air has no rewarming advantage compared to blankets in treatment of mild hypothermia. Forced air results in skin warming, shivering inhibition, and little or no rewarming advantage compared to shivering itself[26].
Although forced air does not increase rewarming rate compared to blankets, it has shown a lower magnitude of afterdrop, reduces the patient's endogenous energy demand, and in contrast to blankets it has the capability of rewarming independently of the patients shivering[26]. Furthermore, several studies have shown that this method is suitable for treating moderate hypothermia and even some case studies show successfully treating severe hypothermia while continuous CPR was performed[12].

The group of invasive methods shows a clear tendency that ECC (venoarterial) has the best performance with a mean of 8,8 °C /h. Pleural lavage is the second fastest rewarming method with an average of 4,7 °C /h in humans. None of these methods has shown any significant afterdrop. As a method for moderate AH, pleural lavage seems to have a high effect regarding rewarming rates and several case reports describe successful treatment of moderate hypothermia using this technique.[21], [27], [28]
Through an article by, Brian R. Plaisier, it was estimated that this method produces a rewarming rate of 2,5-7,5 °C /h[10].
By pooling the data with an additional sample of 28 subtracted from three more articles[19], [21], [28] which included animal case-control studies, a span of 2,4 – 7,5 °C/h was calculated, leaving only a difference of 0,1 °C /h. Therefore, an average rewarming rate of 4,7 °C /h seems likely to be representable for this method. The lower percentile for pleural lavage was identified as a rewarming rate of 2,8 °C /h. Calculated through animal and human studies combined. A comparison between the variance of the mean for all methods would be appropriate for expressing the liability of each method, but due to the lack of representative data, it is not emphasized in this study.

Choosing the right rewarming methods always depends on the situation. But the literature review has shown that ECC is the fastest heater. Furthermore, this method provides the opportunity to oxygenate the blood in case of circulatory collapse. On this basis, ECC is concluded to be the most efficient method to treat severe and moderate hypothermia in patients with imminent risk of circulatory collapse.

A major problem in comparing the different articles is how to measure temperature, and how to define the core temperature? In the hypothermic victim temperature may vary considerably around the body, even under controlled hypothermia during operations [3], [29].

When evaluating the effect of the new device HeatCath, it is appropriate to compare the rewarming rates with pleural lavage as this method tends to be most effective regarding moderate AH according to the literature. Reaching the same high rewarming rate as pleural lavage does not seem possible as pleural lavage fills the entire lung cavity and thereby transfers conductive heat to a relatively large area. Due to this fact it is more realistic for HeatCath to match the lowest rate defined as 25. percentile of the mean rewarming rate which is equal to 2,8 °C/h for pleural lavage.

This leads to the following hypothesis:
By central core rewarming with a new pleural catheter, it is possible to establish a safe and controlled treatment of moderate hypothermia, with rewarming rates equal to or faster than 2,8°C /h, tested in a porcine model.

2 | Method

2.1 | Ethical approval

The Ministry of Food, Agricultura, and Fisheries of Denmark approved the study (number: 2022-15-0201-01298). The first series contains two animals (49 kg and 53kg). On arrival, the animals acclimated for 7 days before experiments were conducted.

2.2 | The design of HeathCath

HeatCath consists of a catheter that is inserted into the lung cavity via a specially designed entry port penetrating the intercostal space. The catheter is designed as a heating blanket with a complex system of small channels. When the catheter is positioned correctly on the surface of the lung, water pressure will unfold the catheter to increase the surface area and consequently start the heat dispersion.
Water flow and temperature are controlled by an external control unit to optimize the rewarming process.

2.3 | Anesthesia and instrumentation

Anesthesia was administered to the fasting animals by an I.M bolus of Zoletilmix 1,5 ml/10 kg *(One ml contains: Tiletamin 8,3 mg, Zolazepam 8,3 mg, Xylacine 8,3 mg, Butorphanol 1,7 mg, Ketaminol 8,3 mg).*
After transfer to the operation room, the animals were placed in a supine position, and the trachea was intubated with a cuffed 7 mm internal diameter tube (Convatec Lim, Deeside, Flintshire CH5 2NU, UK). The lungs were mechanically ventilated by a respirator (Dameca Dream, Rødovre, Danmark) with an initial tidal volume of 8-10 ml/kg and positive end-expiratory pressure of 5 cm H_2O. Rate, tidal volume, and fraction of O_2 was continuously adjusted to maintain arterial PO_2 > 10kPa and to keep $PaCO_2$ at 4.5-5.5 kPa. To confirm adequate ventilation arterial blood gas (ABG) from a carotid catheterization was analyzed on ABL (ABL 90 flex plus, Radiometer, København, Danmark). The same catheter was used for blood pressure monitoring. A CVK was inserted in the left internal jugular vein for drug administration. The anesthesia was maintained by a continuous infusion of Propofol (10 mg/mL set to 15 mL/hour, Frenius Kabi AB, Uppsala, Sverige) and Fentanyl (50 µg/mL set to 15 mL/hour, B.Braun, 34209 Melsungen, Germany) Anesthetic drugs were reduced gradually during the cooling phase. In the case of shivering, 1 ml of Xylazine (20mg/ml) was given intravenously.

Body temperature was measured both in the bladder and intraabdominal. A catheter with a temperature gauge (Mon-a-Therm, foley catheter with temperature sensor 400, by COVIDIEN) was inserted in the bladder for continuous temperature monitoring and measurement of diuresis. A thermometer (Mon-a-Therm, foley catheter with temperature sensor 400, by COVIDIEN) was percutaneously placed in the abdominal cavity adjacent to the liver.

An extracorporeal circuit was established between a femoral vein and a femoral artery using the percutaneous Seldinger technique. A 17 French catheter (Medtronic Inc., Tolochenaz, Switzerland) was inserted in the vein, and a 15 French catheter in the artery. The circuit contained a centrifugal pump (Jostra Rotaflow, Maquet Cardiopulmonary AG, Hirrlingen, Germany) and an ECMO set with an oxygenator and heat exchanger (Jostra Quadrox, Maquet Cardiopulmonary AG). The setup (volume: 300 ml) was primed with saline. Before starting ECC Heparin 25.000 i.u. was administered i.v.
The pleural catheter (HeatCath) was placed bilaterally in the mid-axillary line in the sixth intercostal space. A longitudinal incision of 3-4 cm made access to the insertion port which was mounted with a hermetically closed flank glued directly to the animal's skin. It was then tested if the catheter was able to obtain a flow of 0,7 L/min of water. After completion of the experiment, the animals were euthanized with an intravenous overdose of Pentobarbital (400 mg/ml, total of 20 ml)

2.4 | Experimental protocol

This study serves as the first in a series of experiments that aim to show a significant effect of the pleural catheter, HeathCath. In this first study, two animals are used. One serves as the intervention animal and the other as the control. The two animals were placed in the same room. After instrumentation and 30 min. of stabilization, baseline hemodynamic records were obtained. Both animals were simultaneously cooled down using the extracorporeal systems with a flow of 1,2 L/min. connected to an external cooler. When body temperature reached 26 °C, the extracorporeal systems were disconnected. Another 30 min. of stabilization and baseline hemodynamic records were obtained and the two animals were randomly divided into an intervention group and a control group.
The intervention group was then rewarmed using the pleural catheter until body temperature reached an average of 29 C° measured between the bladder and the abdominal temperature.
The control animal was continuously supported by ventilation and anesthesia. After first part of the study was ended, the control animal was rewarmed using the same technique as the intervention animal, utilizing the opportunity for further test of the equipment, ultimately sparring animals in the following part of the study.

2.5 | Cooling and rewarming

The room temperature was 21-21,5 C°. Lowering the animal's body temperature was done by using an external heater/cooler (Stöckert) connected to the heat exchanger in the oxygenator. The extracorporeal circulation set to an ECMO flow of 1,8 L/min. Blood was cooled until body temperature was 26 degrees calculated as the average between the bladder and the abdominal temperature.
Rewarming was carried out by using the pleural catheter circulating 42-45 °C of water on each catheter with a flow of 700 ml/min.

2.6 | Data sampling

Data were collected every 15 min. Each data sampling was conducted in the following order: Sampling of heart rate (HR), respiration rate (RF), and mean arterial pressure (MAP), blood pressure (BP). Fluids (ml). Diuresis (ml). Recording of body temperature C° (bladder and abdominal), ventilator settings, EtCo2, and FiO2. In addition, arterial blood gas was analyzed every 30 min. (not corrected for temperature).

2.7 | Statistics

Statistical analysis was performed using SPSS statistical software version 28.0.

3 | Results

The time of cooling to a static hypothermic temperature below 26 °C, varied between the two animals.

Pig 1 (later the intervention pig) reached a static hypothermic state at a temperature of 24,6. As pig 2 (later the control pig) reached a static state at a temperature of 25,7 °C. Therefore, a baseline temperature of 25,1 ± 0,55 °C. Cooling time was 46 ± 4 min, and rewarming lasted 195 min.

Before cooling, Pig 2 received potassium (50 mmol) due to hypokalemia, and 15 min. later Atropine (0,5 mg.) due to bradycardia. At the end of the cooling xylazine (1 ml; 20 g/ml) was administered by indication of shivering, as well as an additional 50 mmol potassium iv. for stabilizing further hypokalemia (k^+ = 2,8).

Pig 1 received Atropine (0,5 mg.) by the indication of bradycardia, before cooling, plus 50 mmol potassium iv. for stabilizing hypokalemia of 3,1. During cooling, shivering occurred and was inhibited first by xylazine iv. (1 ml; 20 g/ml) and later rocuronium (5 ml; 10mg/ml). During rewarming another 50 mmol potassium iv. was added, and xylazine 0,5 ml iv. was administered twice.

During rewarming, pH and CO2 were controlled by adjusting the rate of ventilation. The pH of the control pig was kept between 7,34-7,49. CO2 was ranging from 6,06 kPa to 4,0 kPa. The pH of the intervention was between 7,39-7,42 and the CO2 was in the interval of 5,16 kPa to 4,66 kPa.

It must be emphasized that ABG was analyzed without temperature correction and therefore shows greater levels of oxygen and carbon dioxide tension and thereby lower levels of pH, due to the increase of partial pressure when heated to 37 °C in the ABG-analyzer.

The level of lactate, in both the intervention and control, did simultaneously increase during the first 60 min. and decrease after 60 min. of rewarming.

At no point was the lactate beneath 2.0 mmol/L. The control animal presented lactate ranging from 2,3 mmol/L at the beginning of rewarming and peaking to 3,1 mmol/L when reaching 26,9 °C. The intervention animal presented a higher level of lactate during rewarming, initiating with a lactate of 3,7 mmol/L peaking at a level of 4,6 mmol/L witch theoretically would induce metabolic acidosis.

The reason for the high level of lactate is somewhat unclear, but a pinched femoral artery in context to the establishment of ECMO, hench bad perfusion of the leg was suspected, and if the rewarming had any influence on the tissue, the increased cell metabolism would force anaerobic combustion resulting in the lactate levels to rise.

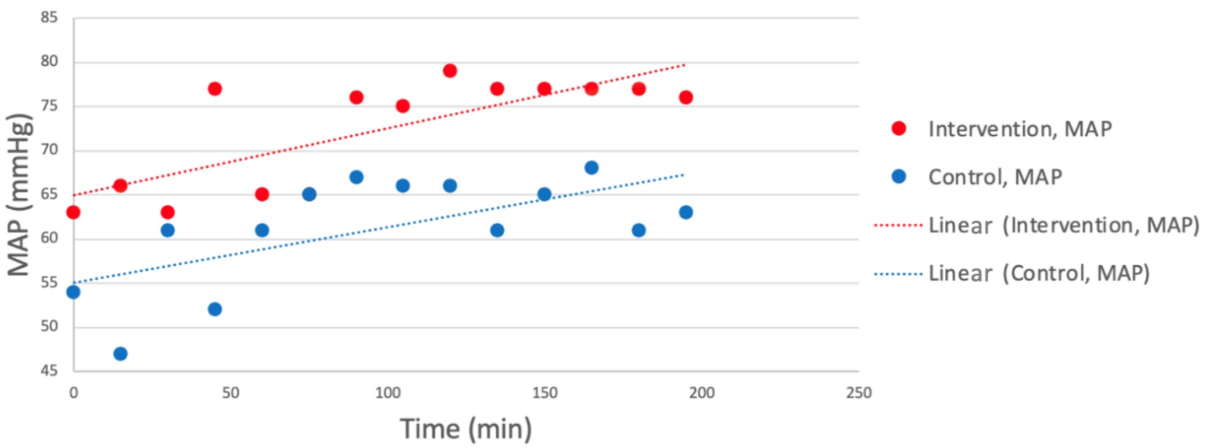


Figure 2: *MAP as a function of time during the 195 min of rewarming. Linear regression has been applied*

3.1 | Hemodynamics (Figure 2,3)

During rewarming the control animal had a mean MAP of 61 mmHg (±7 mmHg) with a heart rate of 57 bpm (±27 bpm) and a blood pressure of 61/49 mmHg (± 9/7 mmHg) (note; normal BP in pigs range from 86-123 systolic and 72-98 diastolic) a sufficient but low MAP was sustained regardless of a low mean BP, no compensatory increase of heart rate was detected, which matches the known physiology when cooled to below 26 °C. During rewarming the intervention animal had a mean MAP of 71 mmHg (± 8 mmHg) with a heart rate of 57 bpm (± 13 bpm) and a BP of 80/55 mmHg (±7/8 mmHg).

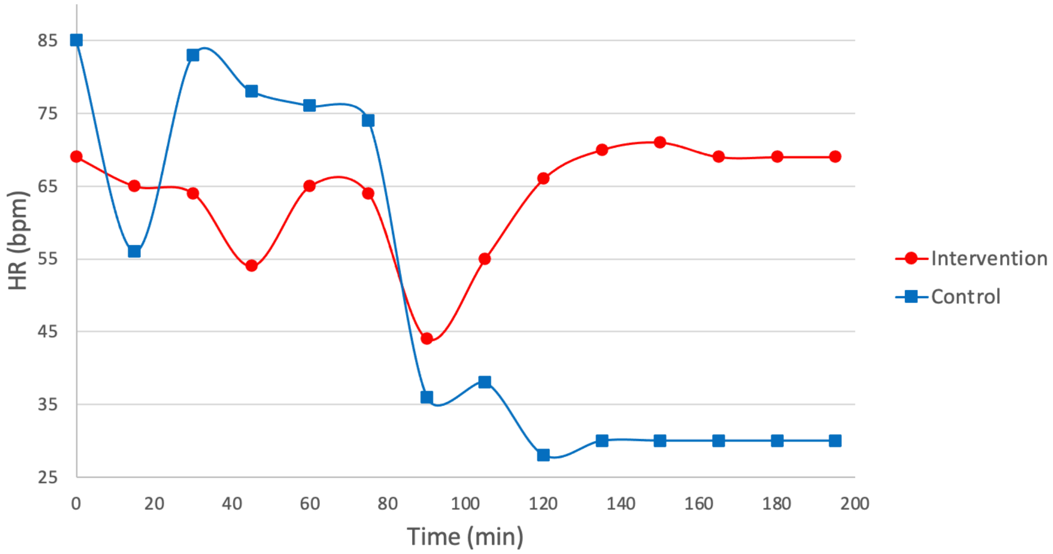


Figure 3: *Heart rate as a function of time during the 195 min of rewarming*

An amount of 3 L of iv. fluids were given, and 750 ml was produced in urinary output, a difference of 2,3 L. regarding input and output. Meaning that the intervention animal was in a more hydrated state which could reflect the somewhat higher BP.

3.2 | Rewarming rate (Figure 4 - 5)

On Figure 4 the mean temperature of the bladder and the abdomen is plotted as a function of time, during the 195 min of rewarming. The mean rewarming rate in this period was 0,4 °C/h for the control and 1,3 °C/h for the intervention.

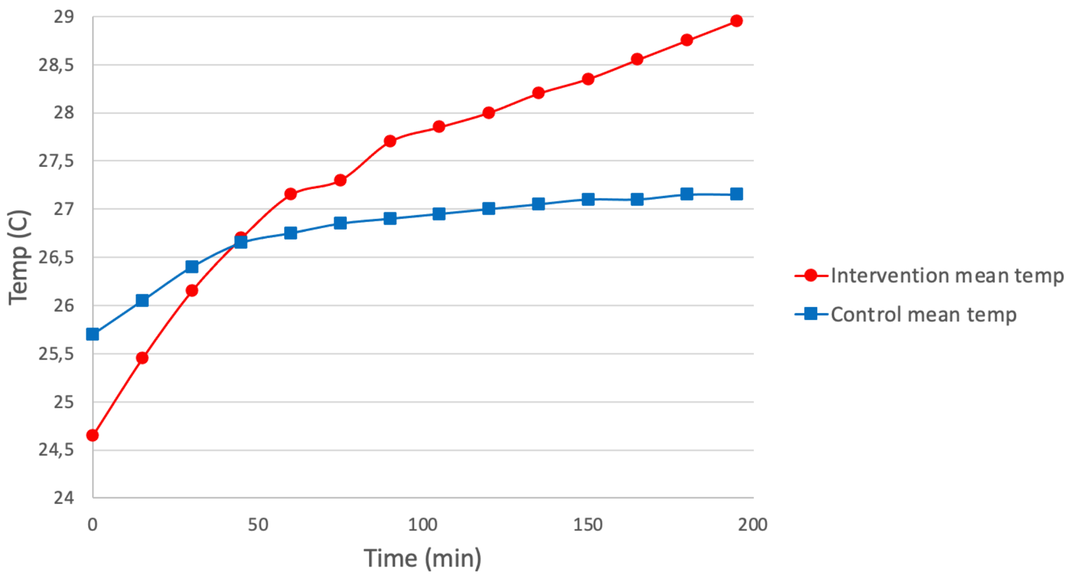


Figure 4: *Rewarming rate as a function of time during the 195 min of rewarming*

The initial temperature was 1,1 C lower in the intervention. To evaluate the rewarming rates from the same temperature starting point, another comparison was done by calculating the average of the rewarming rate from time 45 min. (both the intervention and control were exactly 26,7 °C at this time) to 195 min. During this period the control rewarming rate was 0,2 °C and the intervention was 0,9 °C.

During rewarming of the intervention pig the temperature of water in the catheter was increased from 42 °C to 45 °C at time 135 min. To evaluate the effect of this adjustment, the rewarming rate an hour before the adjustment (time 75 - 135 min.), was compared to the rewarming rate after (time 135 - 195 min.). This showed a decrease in rewarming rate from 0,9 °C/h to 0,75 °C/h even though delta temperature (difference in temperature between core- and the water temperature in the catheter) was increased from 14 °C to 16,5 °C.

After 195 min. of no active rewarming the control pig was treated with 45° C warm water in the pleural catheter. Figure 5 shows the rewarming as a function of time during the control period and 60 min of active treatment. The average rewarming during the period (time 195 - 255 min.) was 1,1 °C/h.

No afterdrop has been detected, at any time, neither in the control nor the intervention pig.

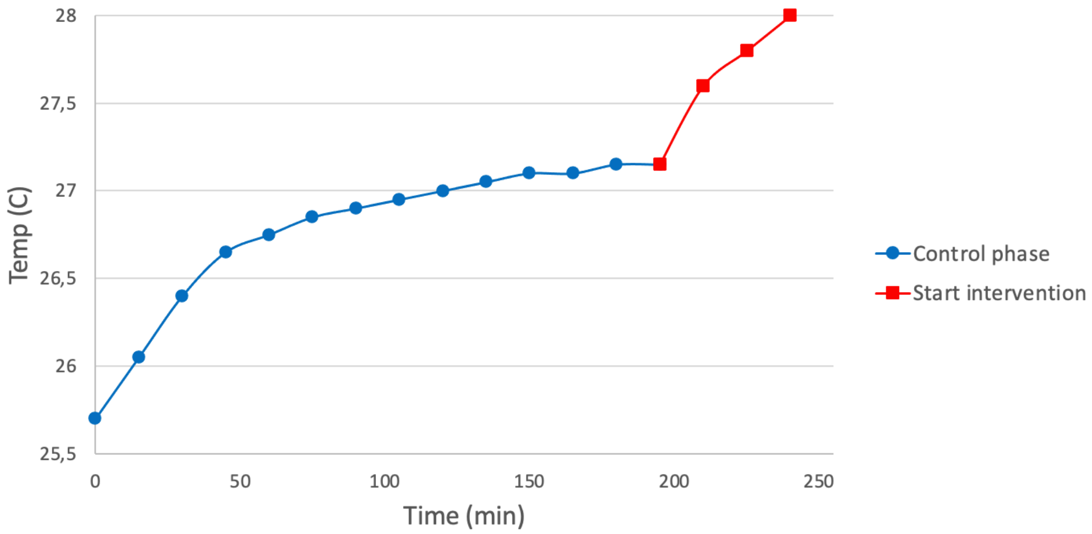


Figure 5: *Rewarming rate as a function of time during the 195 min of control phase and 60 min of active rewarming with HeatCarth*

3.3 | Sample size to show a significant effect

If it is desired to conclude whether the rewarming rate is significantly higher using HeatCath compared to no treatment, a new series of experiments needs to be conducted. To evaluate the sample size of this series, a power analysis, using the Mann Whitney Test was carried out. This indicates that a series of 18 (n=36) is necessary to obtain 95% power of the test with a 95% confidence level. Median values from the experiment are used (Intervention = 1,3 °C/h; Control 0,4 °C /h). Since no standard deviation is available from the first test due to the low sample size. The following assumptions have been made: The standard deviation of rewarming rates from the literature concerning pleural lavage in pig models (n=28) is used as an alternative standard deviation using HeatCath which is 0,7 °C /h. Treating hypothermia using HeatCath did not meet the requirements from the hypothesis to redeem a rewarming rate of 2,8 °C/h.
If new improvements to the device show that these specifications can be achieved with a median value of 2,8 °C/h. A new calculation of the

sample size indicates that a series of 5 (n=10) is necessary to obtain 95% power of the test with a 95% confidence level.

5 | Discussion

This is a pilot study, and the experimental result is based on only two samples. One presented a control group and another presented an intervention group. This means that all outcomes and conclusions aim to show a trend. The trend was then used to conclude if the new device seems to comply with the requirement specifications or if further optimizations had to be done before a greater series of experiments is to be carried out. This approach is considered to be the most ethical and requires the lowest number of pigs.

4.1 | Does rewarming rate matter?

Experimental research on rewarming hemorrhagic shocked rats, shows fewer complications and a smaller mortality rate when rewarmed with a low rewarming rate of 2°C/h versus a high rate of 6°C/h[31]. Similar conclusions are drawn in experiments on rewarming after therapeutic hypothermia in a rat model[32].
Results from such experimental settings are incomparable to the present study but raise questions about the rationale for achieving a higher rewarming rate, which is deficiently described in the literature.

4.2 | Influence of hypothermic state

HeatCath Is intended to be beneficial in the treatment of moderate hypothermia. The classification of the hypothermic stage is defined by a combination of clinical presentation and core temperature. The clinical presentation is hard to determine in an anesthetized animal. After the end of cooling phase, a temperature of 24,6 and 25,7 for the intervention and control group was reached respectively. Considering the temperature alone it is likely that the animals could have been in a state of severe hypothermia. A 0,5 mg Atropine was administered before cooling, and continuous fluids were given which could mask a potential circulatory instability. On the other hand, regardless of having a half-life of 4 hours, atropine is anticholinergic and should have a refractory effect on any bradydysrhythmia developed in a hypothermic state, since the bradycardia is cursed by decreased spontaneous depolarization of the pacemaker cells and not increased vagal tone.
However, many pathophysiology changes are temperature dependent and in tight relation to the different signs and symptoms seen in the different stages of hypothermia. Circulatory collapse is prone to occur by many factors e.g., cardiogenic factors such as ventricular dysrhythmias, and reentrant dysrhythmias which are provoked by decreased conduction velocity in combination with increased myocardial conduction time and a decreased absolute refractory period. The conduction system has an increased sensitivity to cold temperatures compared to the myocardium resulting in a prolonged cycle. Below 25 °C the cardiac output is 45% of normal. All leading to a potential circulatory collapse. By around 24 °C a significant hypotension is likely to present, due to the blunted catecholamine release leading to peripheral vasodilatation and further cooling of the blood, simultaneously an inhibition of catecholamine leads to the further reduction in heart rate.[33]
There is inevitably a causality between temperature and the severity of hypothermia over time. Taking the above-mentioned into consideration one could argue that an animal cooled to 24,6 °C is in a severely hypothermic state and very likely to become unstable if not supported, furthermore the metabolic rate of cells is drastically decreased at this temperature. It is scarcely described in the literature if it requires a prolonged time to reheat the body in these pathophysiological conditions below 28 °C, and if so would HeatCath perform better if the baseline temperature never drops below 28 °C?

4.3 | The effect of increasing water temperature in the catheter

During the development of HeatCath, it was assumed that the fastest rewarming rate was achieved by increasing the water temperature in the catheter as much as possible but without any risk of tissue damage. The initial temperature was 42 °C but during the rewarming period, the delta temperature was increased by increasing the water temperature to 45 °C. Against expectations, this had a slightly negative effect on the rewarming rate. This might be related to the fact that the temperature of the animal was a bit warmer and thereby, according to the thermodynamic laws, conducts more heat to the surroundings. Another explanation is due to simple deviations in the temperature measurements, which might be different if experiments were repeated.
It might be possible to proceed using 45 C of water in the catheter. A report concerning "tracheal burning from hot air inhalation" states that no damage will occur if the temperature is kept at a maximum of 45 °C [34].
If it is decided to increase the catheter temperature to 45 °C it is necessary to look for tissue damage after ending the experiments. A biopsy of the effected area would be appropriate to investigated if the tissue suffer any irreversible damage.

5 | Strengths and limitations

Strengths: To improve the quality of the pilot study the two trial subjects were not categorized as control or intervention pigs until the rewarming phase was started. The selection of the two categories was done by coinflipping to ensure randomization. The study was furthermore performed under experimental settings which limits the risk of certain confounders.

Limitations: Due to the sample size of two subjects, it is difficult to predict the quality and the reproducibility of future studies. Due to the nature of a pilot study, it serves as guidance to whether there is an incentive for further studies and whether the results are necessary for a power calculation estimating the future sample size. The results are therefore less unambiguous and require several repetitions. The product is for use in humans but is tested in pigs. There are some differences between pigs and humans, despite the great comparisons of anatomy and physiology. Therefore there is no guarantee of achieving the same results if transferred to humans.

6 | Conclusion

We consider both animals to be equally representative of moderate to severe hypothermia, regarding temperature, biochemical and vital signs. If compared to the control animal parameters such as MAP and HR could indicate a small tendency towards a more stable outcome, and none of the other measured parameters arouse any suspicion of the intervention pig performing worse than the control pig.
The intervention did perform better than the control animal regarding rewarming rate. Warming at a rate of 1,3 °C/h which is 0,9 °C/h greater than the control during the rewarming time of 195 min. The intervention had a lower baseline temperature of 1,1 °C which could influence the comparison of rewarming rate. Increasing the input temperature of water from 42°C to 45°C expressed a small decrease in rewarming rate of 0,15 °C/h. When starting treatment with HeatCath on the control animal after 195 min. at a temperature of 27,1°C a rewarming rate of 1,1 °C/h was observed, meaning an increase in the rate of 0,7 °C/h (1,1°C ÷0,4 °C).
HeatCath has displayed functional and controlled rewarming capacities, but HeatCath has not yet met the criteria of a rewarming rate of 2,8 °C/h.

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