Active internal re-warming using a centrifugal pump and heat exchanger following haemorrhagic shock, surgical trauma and hypothermia in a porcine model

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Summary

Background: The centrifugal vortex blood pump (CVBP) using heparin-bonded circuitry allows re-warming of hypothermic trauma patients without anticoagulation. Study objectives were to confirm efficacy, and to characterise the physiology of CVBP re-warming in a porcine model.

Methods: Sixteen pigs were randomised to conventional or CVBP re-warming. They were bled to a mean arterial pressure of 30 mmHg and cooled to 29°C. A physiological analysis was recorded during resuscitation to normotension and re-warming back to 37°C.

Results: CVBP animals re-warmed significantly faster: 85.0 ± 16.4 min versus 217.4 ± 49.3 min (p < 0.0001). Activated clotting time was significantly elevated in both groups at 29°C with a marked trend to normalise faster in CVBP pigs. The peak cardiac index (CI) was significantly lower (1.14 ± 0.68 versus 4.83 ± 1.50 L/min m²), while the systemic vascular resistance (SVR) was significantly higher (4239.9 ± 1173.0 versus 1472.6 ± 451.2 dyn s cm⁻⁵) with CVBP (p < 0.001).

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Introduction

Hypothermia, defined as a core body temperature of <36 °C, contributes significantly to adverse physiological changes which affect homeostasis, and if severe enough, results in progressive organ and systemic dysfunction. In some instances hypothermia can provide an overall protective effect on the body but in trauma, hypothermia is recognised as one pillar in the “lethal triad” of hypothermia, coagulopathy, and acidosis. Hypothermia compounds the effects of coagulopathy and acidosis leading to hypoxia, electrolyte imbalances, myocardial depression and cardiac irritability. Clinical reviews of trauma patients have indicated a strong association with hypothermia and mortality to the extent that those who have a core temperature of <32 °C do not survive. Classically hypothermia has been graded as mild, moderate, or severe; however, Kirkpatrick et al. have proposed a classification more relevant to the trauma population where mild hypothermia has been further subdivided into Class I (>34 °C) and Class II (34 °C—32 °C), which reflect the distinct effects of hypothermia on trauma patients.

Given the deleterious nature of hypothermia in the trauma setting, it is logical to assume that attempts to minimise heat loss and provide heat gain might benefit the injured patient. Methods by which heat losses are minimised and heat gain is maximised fall into two groups: passive and active rewarming. Both methods may be applied externally or internally.

In active rewarming, external techniques such as warming blankets and warmed-air blankets actively warm the immediate external environment to decrease temperature gradients thus diminishing convection and radiation losses. Internal techniques include the use of warmed intravenous fluids, warmed inspired gases, and intracavitary lavage with warmed fluids. All of these techniques have been shown to reduce temperature loss and to allow slow temperature gains. However, they rely on the body’s ability to generate heat in order to maintain and raise core temperature.

The most efficient means of warming a patient is to actively warm the blood. The technique of rewarming with cardiopulmonary bypass is long established, effective, and safe in the setting of severe hypothermia. It is limited in the trauma patients due to the complexity and availability of the current equipment, the need for cardiothoracic surgical support, and the need for systemic anticoagulation.

Gentilello et al., have described a simple technique to provide extracorporeal blood warming known as continuous arteriovenous re-warming (CAVR). No pump is required as the patient’s blood pressure drives the system. One obvious problem with this is that in severely injured patients their systemic pressure may be too low for CAVR to be effective.

Recently, another system has been identified that can provide rapid active blood warming without systemic anticoagulation. The centrifugal vortex blood pump (CVBP) using heparin-bonded circuitry and a heat exchanger allows a veno-venous bypass system to be created, which can produce high-flow rapid re-warming without anticoagulation. This has been demonstrated both in a dog model and in a small human series where re-warming times as fast as 30—60 min have been documented.

The aims and objectives of this study were three-fold; to confirm the efficacy and to characterise the physiology associated with CVBP rewarming and finally to determine any problems associated with the technique.

Methods

This study was approved by the University of British Columbia and Vancouver Hospital Research Ethics Board Committees on Animal Care.

Sixteen female Yorkshire pigs between 50 and 70 kg were randomly assigned to either conventional (n = 8) or experimental CVBP (n = 8) re-warming. The animals were fasted overnight but were allowed to drink water freely. Anaesthesia was induced with intramuscular ketamine (10 mg/kg) followed by endotracheal intubation and ventilation with a Drager AV system ventilator (Drager North America, Telford, PA). Anesthesia was maintained with an intravenous infusion of Diprivan (Propofol) at 200 μg/(kg min). They were also given intramuscularly Buprenorphine (Temgesic) 0.01 mg/kg for analgesia.

Conclusion: CVBP is simple and very effective at re-warming hypothermic animals and may also reverse coagulopathy more quickly. Physiological derangements of elevated SVR and diminished CI require further study to elaborate underlying aetiology, and define optimal re-warming strategies.
The ECG was monitored continuously. Maintenance fluids were provided intravenously with lactated Ringer’s solution, given at a standardised rate: (total for a 24 h period: first 10 kg:100 cm³/kg; next 10 kg:50 cm³/kg; 10 cm³/kg thereafter). The core temperature was measured continuously using an oesophageal probe and thermometer (Tele-Thermometer Model 44TD or Model 49 TA, Yellow Springs Instrument Company, OH). Normothermia was maintained with a warming blanket set to 41 °C (Solid State Aquatic Kthermia RK-600, Gormann Rupp Industries, Belleville, OH). An indwelling suprapubic urinary catheter was inserted after the laparotomy to measure urine output.

Left carotid arterial cannulation was performed for continuous blood pressure monitoring. A 14-gauge angiocatheter in the left jugular vein was used for fluid infusion. The right jugular vein was isolated with vessel loops in preparation for subsequent ligation (control animals) or bypass cannulation (CVBP animals). Cannulation of the left femoral artery with a 16-gauge angiocatheter was performed to rapidly bleed the animal to achieve haemorrhagic shock. The right femoral vein was isolated with vessel loops in preparation for ligation (control animals) or bypass cannulation (CVBP animals). A pulmonary artery (PA) catheter was inserted in the left femoral vein and floated into the PA.

After placing the lines, rapid phlebotomy was performed and titrated to reduce the mean arterial pressure (MAP) to 30–35 mmHg inducing haemorrhagic shock. The blood was collected into standard citrated blood collection bags and placed into a water bath set at 39 °C (Napco 230A, National Appliance Company, Portland, OR) for later re-infusion. Further bleeding or replacement of shed blood could begin as there would be insufficient venous return. In our current experiment, the animals received the initial bolus of LR and half the shed blood before the pump was turned on. The primary experimental end-point was time to the attainment of a core temperature of 37 °C. The study pigs were left on bypass for 30 min after reaching this goal to prevent after-drop in their core temperature as demonstrated in pilot studies (unpublished data).

The following parameters were monitored continuously and recordings taken at 15-min intervals: ECG, pulse rate, systemic blood pressure (systolic, diastolic, mean), pulmonary artery pressure (systolic, diastolic, mean), and temperature. Urine output was measured hourly. Arterial blood samples from the left femoral arterial line as well as haemodynamic parameters using a pulmonary artery catheter were taken at set temperature intervals—baseline: 35, 32, 29, 30, 32, 34, 36, and 37 °C. Blood samples were analysed using an i-STAT (i-STAT Corp., East Windsor, NJ) and a Hemochron blood coagulation timer (model 401, International Technidyne Corp., Edison, NJ) for complete blood count, electrolytes, arterial blood gas, and activated clotting time (ACT) determinations.
Upon completion of the study protocol, all animals were euthanised with 90 mg/kg of pentobarbital administered intravenously (Euthanal, Biomedica, Cambridge, Ont.). An autopsy was performed on all animals looking for thrombus formation in the IVC, SVC, right heart, and PA. The cannulae and pump circuitry were also examined for thrombus accumulation.

Statistical significance was evaluated at the \( \alpha = 0.05 \) level. All variables were reported as mean \( \pm \) S.D. and with their 95% confidence intervals. The ANOVA statistical model was used to compare all continuous variables of interest, from the independent samples of two groups: the control versus study (CVBP).

Results

Characteristics for the animals in each group were similar with regards to weight, total volume of blood loss, time required to cool, lowest temperature achieved, and lowest MAP reached (Table 1). The control animals, which were re-warmed using conventional means, required a significantly greater length of time to achieve normothermia compared to the study animals (Table 2 and Fig. 1). The mean time on CVBP was 80.4 \( \pm \) 26.6 min with a mean peak flow of 2.6 \( \pm \) 0.4 L/min. The study pigs required more IV fluid resuscitation with Ringer’s lactate but this was not significant. There were no significant differences in serum sodium, and potassium between control and study animals at any of the measured temperature intervals. There was also no significant difference in the haemoglobin (Hb) during the cooling/bleeding phase but it was significantly lower in the study group during all phases of re-warming. Activated clotting time was significantly elevated in both groups at 29 \( ^\circ \)C with a trend to return to normal faster in the study pigs (Fig. 2). The cardiac index (CI) of the study group while on CVBP was significantly lower than controls with a peak difference of 1.14 \( \pm \) 0.68 versus 4.83 \( \pm \) 1.50 L/(min m\(^2\)). This returned to normal as they became normothermic (Fig. 3). The systemic vascular resistance (SVR) was also significantly higher in the study group while on pump with a peak difference of 4239.9 \( \pm \) 1173.0 versus 1472.6 \( \pm \) 451.2 (dyn s/cm\(^5\)) (Fig. 4).

There was one death in the study, and it was in the active re-warming group. The pig died 2 min after starting veno-venous bypass. An autopsy

Table 1 Characteristics for both control and study groups

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 8)</th>
<th>Study group (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Animal weight (kg) ( \pm ) S.D.</td>
<td>62.0 ( \pm ) 5.4 [57.5—66.5]</td>
<td>61.1 ( \pm ) 6.4 [55.3—67.0]</td>
</tr>
<tr>
<td>Base temperature ( ^\circ )C ( \pm ) S.D.</td>
<td>37.0 ( \pm ) 0.8 [36.3—37.6]</td>
<td>37.0 ( \pm ) 0.7 [36.4—37.7]</td>
</tr>
<tr>
<td>Volume of blood shed (mL) ( \pm ) S.D.</td>
<td>1312.5 ( \pm ) 350.3 [1019.7—1605.3]</td>
<td>1350.0 ( \pm ) 178.0 [1019.7—1605.3]</td>
</tr>
<tr>
<td>Volume of blood shed as percentage of estimated blood volume (%) ( \pm ) S.D.</td>
<td>35.7 ( \pm ) 10.9 [26.5—44.8]</td>
<td>37.4 ( \pm ) 8.2 [29.8—45.0]</td>
</tr>
<tr>
<td>Duration of time with MAP ( \leq 35 \text{ mmHg} ) (min) ( \pm ) S.D.</td>
<td>38.4 ( \pm ) 17.2 [24.0—52.8]</td>
<td>43.3 ( \pm ) 20.3 [24.5—62.1]</td>
</tr>
<tr>
<td>Time required to cool animals to 29 ( ^\circ )C (min) ( \pm ) S.D.</td>
<td>87.6 ( \pm ) 19.0 [71.7—103.5]</td>
<td>77.3 ( \pm ) 14.7 [63.7—90.8]</td>
</tr>
<tr>
<td>Lowest temperature reached ( ^\circ )C ( \pm ) S.D.</td>
<td>28.4 ( \pm ) 0.5 [28.0—28.9]</td>
<td>28.7 ( \pm ) 0.2 [28.5—28.8]</td>
</tr>
<tr>
<td>Lowest MAP (mmHg) ( \pm ) S.D.</td>
<td>33.4 ( \pm ) 4.1 [29.9—36.8]</td>
<td>31.6 ( \pm ) 4.3 [27.6—35.5]</td>
</tr>
</tbody>
</table>

n: number of animals; S.D.: standard deviation; 95% CI: 95% confidence interval.

Table 2 Time to re-warm and total resuscitation IV fluid

<table>
<thead>
<tr>
<th></th>
<th>Control group (n = 8)</th>
<th>Study group (n = 7)</th>
<th>p-Value</th>
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<tbody>
<tr>
<td>Time required to re-warm animals to 37 ( ^\circ )C (min) ( \pm ) S.D.</td>
<td>217.4 ( \pm ) 49.3 [171.8—263.0]</td>
<td>85.0 ( \pm ) 16.4 [62.8—100.2]</td>
<td>0.000021</td>
</tr>
<tr>
<td>Total fluid requirement (mL) ( \pm ) S.D.</td>
<td>6793.8 ( \pm ) 3135.3 [4172.5—9414.9]</td>
<td>9942.9 ( \pm ) 4148.0 [6106.6—13779.1]</td>
<td>0.118</td>
</tr>
</tbody>
</table>

n: number of animals; S.D.: standard deviation; 95% CI: 95% confidence interval.
revealed no specific cause of death; however, a malfunction in the warming bath used to store the autologous shed blood was discovered. This had caused the temperature to be set at 50 °C with probable lysis of red blood cells, which were infused just before bypass had begun. The animal’s arterial potassium was measured at 7.0 just after cardiac arrest occurred and is considered the likely cause of death. This malfunction was not related to the use of the CVBP and this pig was therefore excluded from analysis.

Discussion

Hypothermia accentuates the physiological consequences of anatomic injury, and when severe (<32 °C), results in high mortality. A prospective, randomised trial of re-warming found all trauma patients that failed to re-warm died early. Temperature dependant enzymes catalyse many physiological processes that contribute to the maintenance of homeostasis. There are also significant derangements in microcirculation and tissue metabolism in hypothermia that may not fully recover with re-warming. The physiological implications of hypothermia are that overall metabolism is slowed, and functions related to cardiac activity, electrolyte balance, and coagulation are impaired, increasing mortality.

Various methods of re-warming exist, and can be broadly classified into passive and active, external and internal methods. The most commonly used methods are passive external and internal re-warming. Controlling the patient’s environment by raising the ambient temperature, the use of warmed-air blankets (‘Bair Huggers’), and covering the patient’s body with warm blankets protect against heat loss and may transfer a small amount of heat to the patient. The use of warmed intravenous fluids is an example of passive internal re-warming.

Active re-warming has been achieved with intracavitary lavage involving the infusion of warmed fluids into the stomach, peritoneal cavity, pleural cavity or bladder in an attempt to transfer heat to the body core. These have been largely abandoned given the questionable gain in overall core temperature elevation or their overly invasive nature. Cardiopulmonary bypass has been proven to be both effective and safe method of active core re-warming in the context of cardiac surgery. In trauma patients, the need for systemic anticoagulation and the technical complexities that require specialised equipment and personnel to operate effectively are major drawbacks.

Gentilello and others have described the use of rapid fluid infusers adapted to provide arterio-venous bypass and countercurrent warming of patient blood. This was a significant advance in re-warming hypothermic trauma patients. The major disadvantage of this technique, however, is that it is applicable only to normotensive patients. In the severely injured, hypotensive and hypothermic patient, CAVR may not be possible.

Hiles et al. used another type of fluid rewarmer to perform veno-venous re-warming on a hypothermic pig model. They demonstrated a significant improvement over standard re-warming techniques with potentially less morbidity than CAVR.

An improvement on the use of rapid infusers and heat exchangers is to incorporate an external pump and heparin-bonded circuitry. The motive force for blood circulation is now no longer dependent on the patient, and the use of heparin-bonded circuitry
obviates coagulation problems in the pump and tubing. The centrifugal pump system, introduced in 1974, has been in use for many years in cardiac surgery, and has been shown to be safe and effective in producing high laminar flow rates and low haemolysis of blood cells. The system is also much simpler to set up and operate compared to full cardiopulmonary bypass, and is considerably cheaper. High flow rates can be achieved without difficulty and the ease of attaching a heat exchanger, and membrane oxygenator as desired, has made this system very attractive for applications in traumatic injury and hypothermia. Janczyk et al. have used this technique in a dog model with good results.11 Our group has described a series of 7 severely injured, hypothermic patients with which CVBP was used to re-warm them in the operating room as part of damage control surgery.14 We observed an ultimate survival rate of 43% comparing favourably with historical survival rates.12

The current study investigated the physiology of using the active CVBP re-warming system in a porcine trauma model. We used the warming blanket and warmed IV fluids as standard (control) therapy since these techniques are routinely and exclusively used in many institutions. From a technical viewpoint the methodology of CVBP is simple and straightforward to apply and in this and previous clinical studies, cannulation and circuit set up has been performed by general surgeons without cardiothoracic support. Cannulation of vessels with tubing of sufficient size (16 F) to support adequate flow rates of the pump was not difficult. In addition, percutaneous placement of these catheters is possible.14,16,27 Our level one Trauma Centre has a perfusionist on call 24 h but trauma nurses have been trained to set up and run the CVBP system in other centres.11 Extremely rapid re-warming times were possible, with a rise in oesophageal temperature of the study animals from 29 to 37 °C attained in as little as 66 min. This compares favourably to reported CAVR and CVVR warming rates.5—11 The rapid rise in temperature appears to correct the coagulopathy sooner and therefore may reduce the danger of ongoing exsanguination. The lack of statistical significance of this effect is probably due to the small number of pigs enrolled into each arm of the study, the number of temperature points measured, as well as the way we measured ACT. The blood sample is re-warmed by the machine to 37 °C as the ACT is measured. This could artificially reduce the effects of hypothermia on coagulation. Shimoskawa et al. demonstrated this problem, and found re-warming the blood samples underestimated the severity of coagulopathy.23 They used temperature adjusted thromboelastography1 (TEG)1 to correctly estimate the coagulopathy and this method would be useful in further experiments.

Although markedly effective at re-warming, notable physiological derangements were observed with CVBP re-warming, indicating a need for caution. The CI was considerably decreased and the SVR was consistently increased with CVBP. These measurements were consistent with the physical findings of mottling and increased fluid requirements. These haemodynamic characteristics may have been due to the nature of the CVBP circuitry. The cannulae were placed into the superior vena cava (SVC) and inferior vena cava (IVC) via more distal veins. The mean peak flow of the pump during the experiment was 2.6 ± 0.4 L/min and system outflow from the IVC may have reduced preload by causing a “vena cava steal” from the inflow into the SVC. This possibility was tested on a separate pig using fluoroscopy and IV contrast to assess blood flow to the heart. A blush of contrast could be seen diverting
back down the IVC from the SVC. In this same pig we clamped the suprarenal IVC above the outflow cannula and noted an increase in cardiac index from 1.36 to 3.25 L/(min m²) with no other intervention. This phenomenon may only occur in severely hypothermic pigs, as the right ventricle will be less compliant and unable to tolerate the sudden increase in venous return when on CVBP. It was noted that the CI started to rebound to more normal levels in the pigs on CVBP once temperatures reached 36°C. The "vena cava steal" would also explain why we found a trend to more fluid requirements in the study pigs than controls, opposite to what would be expected.6

The lower Hb noted in the study pigs is probably explained by their increased IV fluid requirements. There was no blood used for resuscitation other than what was removed from the pigs, therefore a dilution effect was created. In addition, the CVBP system was primed with 500 ml of plasmalyte, which would cause an additional dilution of the intravascular space. The possibility of haemolysis related to the extracorporeal circulation was also considered. This theory was not supported though, as there was no significant difference in serum potassium levels between the two groups.

This study has shown that CVBP is a feasible and rapid means of re-warming. However the fact that neither control nor study animals were revived and allowed to recover does limit the interpretation of the study to a certain degree. There was no way of demonstrating any obvious long-term deleterious effects of rapid re-warming in the study animals. Another limitation of this model, as with other models of hypothermia, was that standardised rates of re-warming were difficult to achieve and the maximum flow rate achievable was used in this study when setting up the CVBP. Alam et al. developed an interesting pig model where rapid profound hypothermia was induced to facilitate repair of lethal injuries.1 They rewarmed their animals with cardiopulmonary bypass and found that long-term survival was influenced by the rate of re-warming. Further study into the ideal rate of re-warming with CVBP is warranted. Another problem we encountered was that the PA catheter would dislodge when the CVBP was started due to the probable CVBP related turbulent flow. The catheter would have to be repositioned several times before readings could be taken making it a rather temperamental method of measuring cardiac outputs.

In conclusion, our model has demonstrated that veno-venous bypass with CVBP is relatively simple to perform and very effective at rapidly re-warming. Another pillar of the lethal triad (coagulopathy) also appears to be reversed more quickly although not statistically significant in this experiment is felt to be a real effect. The data support preliminary clinical studies suggesting a valuable role for CVBP in clearly defined patients at risk. The findings of profoundly elevated SVR and a diminished CI in CVBP animals mandate some caution in applying this technology. Whether these findings can be explained by the vena caval steal syndrome alone and corrected, or if this is another as yet undefined compensatory effect to CVBP in the porcine model needs to be the subject of further study along with the definition of optimal re-warming gradients and flow rates.

**Conflict of interest statement**

There is no conflict of interest for all the authors of this paper.

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