Thesis

Comparative Analysis of the Efficacy of Four Pressure Infusion Devices in Warming Cold Fluids

An In Vitro Study

submitted by

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Graz, 28/03/2026

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Graz, 28/03/2026 Sonja Öhner, m.p.

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2 Zusammenfassung

Hintergrund: Die schnelle Verabreichung von Flüssigkeiten, beispielsweise bei Schockzuständen, starken Blutungen oder bei einem Reperfusionssyndrom im Rahmen von Lebertransplantationen, kann entscheidend für das Überleben von Patient*innen sein. Dabei kann die rasche Infusion kalter Flüssigkeiten zu einer Hypothermie führen, welche das Outcome der Patient*innen erheblich verschlechtert, indem sie die Herzleistung, den Medikamentenstoffwechsel, die Gerinnung und die Wundheilung negativ beeinflusst und das Infektionsrisiko erhöht. Um derartig schwerwiegende Komplikationen zu vermeiden, sollten Flüssigkeiten vor der Verabreichung auf Körpertemperatur erwärmt werden, auch bei hohem Fluss.

Zielsetzung: Ziel dieser Studie war es, die Erwärmungskapazität, gemessen an der mittleren Temperatur während eines vierminütigen Testzeitraums, von vier verschiedenen Rapid-Infusion-Systemen (RIS) beim Erwärmen einer 4-6 °C kalten Kochsalzlösung sowie von Erythrozytenkonzentraten unter High-Flow-Bedingungen in vitro zu bewerten.

Material und Methoden: Unter Laborbedingungen wurde die Fähigkeit der getesteten Geräte zur Erwärmung von kalter Kochsalzlösung und Erythrozytenkonzentraten (je 4-6 °C) bei hohen Flussraten (~ 500 mL/min) untersucht. Die Temperatur wurde dabei kontinuierlich in Einsekundenintervallen vor und nach der Erwärmung gemessen.

Die folgenden Geräte wurden in der Studie untersucht:

- **AutoMer II** (Ace Medical, Seoul, Südkorea)
- **Belmont® Rapid Infuser RI-2** (Belmont Medical Technologies, Billerica, MA, USA)
- **Fluido® AirGuard** (TSC Life, Amsterdam, Niederlande)
- **3M™ Ranger™** (Solventum Corporation, Maplewood, MN, USA)

Ergebnisse: Bei den Tests mit kalter Kochsalzlösung erreichte nur der Belmont® unter hohen Flussraten physiologische Temperaturen (37,9 °C), während die anderen Geräte Temperaturen von nur 20-29 °C erzielten.

Auch bei den Tests mit kalten Erythrozytenkonzentraten war der Belmont® das einzige Gerät, welches annähernd die Zieltemperatur erreichte und dabei auch eine hohe Flussrate von etwa 480 mL/min verabreichen konnte.

Schlussfolgerung: Es zeigt sich, dass von den getesteten Geräten ausschließlich der **Belmont® Rapid Infuser RI-2** eine effiziente und zuverlässige Erwärmungsleistung unter High-Flow-Bedingungen garantiert. Dies unterstreicht, wie wichtig die Auswahl eines geeigneten RIS ist, um das Risiko einer Hypothermie bei kritisch kranken Patient*innen zu minimieren.

3 Abstract

Background:

The rapid administration of fluids, for example, in shock states, major haemorrhage, or during reperfusion syndrome in the context of liver transplantation, can be critical for patient survival. However, the rapid infusion of cold fluids may lead to hypothermia, which can significantly worsen patient outcomes by adversely affecting cardiac performance, drug metabolism, coagulation, and wound healing, as well as increasing the risk of infection. To avoid such serious complications, fluids should be warmed to body temperature prior to administration, even at high flow rates.

Objective:

The aim of this study was to evaluate the warming capacity – measured as the mean temperature over a four-minute test period – of four different rapid infusion systems (RIS) when warming saline solution at 4-6 °C as well as packed red blood cells under high-flow conditions in vitro.

Materials and Methods:

Under laboratory conditions, the ability of the tested devices to warm cold saline solution and packed red blood cells (each at 4-6 °C) at high flow rates (~500 mL/min) was assessed. Temperature was measured continuously at 1-second intervals before and after warming.

The following devices were investigated in the study:

- AutoMer II (Ace Medical, Seoul, South Korea)
- Belmont® Rapid Infuser RI-2 (Belmont Medical Technologies, Billerica, MA, USA)
- Fluido® AirGuard (TSC Life, Amsterdam, Netherlands)
- 3M™ Ranger™ (Solventum Corporation, Maplewood, MN, USA)

Results:

In tests with cold saline solution only the Belmont® achieved a physiological temperature (37.9 °C) at high flow rates, whereas the other devices reached only 20-29 °C.

Similarly, in tests with cold-packed red blood cells the Belmont® was the only device that approached the target temperature while also delivering a high flow rate of approximately 480 mL/min.

Conclusion:

Among the tested devices only the Belmont® Rapid Infuser RI-2 demonstrated efficient and reliable warming performance under high-flow conditions. This highlights the importance of selecting an appropriate RIS to minimise the risk of hypothermia in critically ill patients.

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4 Index of Abbreviations

ACS	Acute Coronary Syndrome
ADH	Antidiuretic Hormone
AKI	Acute Kidney Injury
ANP	Atrial Natriuretic Peptide
ARDS	Acute Respiratory Distress Syndrome
CPB	Cardiopulmonary Bypass
CPP	Cerebral Perfusion Pressure
DIC	Disseminated Intravascular Coagulation
ECG	Electrocardiogram
FFP	Fresh Frozen Plasma
GABA	Gamma-Aminobutyric-Acid
HB	Haemoglobin
HCA	Hypothermic Cardiac Arrest
HCT	Haematocrit
HES	Hydroxyethyl Starch
HR	Haemolysis Rate
IL-1β	Interleukin-1 Beta
IL-6	Interleukin 6
IQR	Interquartile Range
IRI	Ischaemic Reperfusion Injury
MAP	Mean Arterial Pressure
MOF	Multiple Organ Failure
NO	Nitric Oxide
NOAC	New Oral Anticoagulants
NSAID	Nonsteroidal Anti-Inflammatory Drugs
PAE	Pulmonary Artery Embolism
PAMP	Pathogen-Associated Molecular Patterns
PC	Platelet Concentrates
PiCCO	Pulse Index Continuous Cardiac Output
PMS	Mean Systemic Pressure
PRBC	Packed Red Blood Cells

PRS	Post-Reperfusion Syndrome
RAAS	Renin-Angiotensin-Aldosterone-System
RIS	Rapid Infusion Systems
SBP	Systolic Blood Pressure
SD	Standard Deviation
TBI	Traumatic Brain Injury
TBSA	Total Body Surface Area
TEE	Transesophageal Echocardiography
TIC	Trauma-Induced Coagulopathy
TNF	A – Tumor Necrosis Factor Alpha
VF	Ventricular Fibrillation

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7 Introduction

7.1 Physiology

To fully understand the use and impact of rapid infusion systems in clinical practice it is important to examine the underlying physiology of the human body.

7.1.1 Volume regulation

Volume regulation is necessary to maintain a constant blood volume and to ensure a balance between intracellular and extracellular fluids. The blood volume depends on the lean body mass of a human and is about 3.6 litres in females and 4.5 litres in males. The majority of the volume is located in the low-pressure-system of the blood vessels in which significant volume shifts are possible due to pressure or vein tone changes. (1)

In the event of an acute decrease of blood volume, for example due to acute bleeding, the short-term volume regulation will be activated: venous stretch receptors and arterial pressoreceptors induce a disinhibition which leads to an increase of sympathetic activity and furthermore to arteriolar constriction (see Figure 1). (1)

In case of a decreased intravascular volume, fluid is absorbed from the tissue and the lymphatic veins. According to the classic Starling Principle, absorption in the capillary bed takes place through osmotic and hydrostatic pressure differences. However, recent research shows that there are additional haemodynamic mechanisms that have a major influence on volume distribution: The glycocalyx, a recently discovered fourth vascular layer, is only permeable to an ultrafiltrate that contains just a few macromolecules, such as albumin. It contributes up to 60% to the osmotic pressure and, therefore, limits the reabsorption of fluid from the interstitium. As a result, the majority of the required volume is absorbed from the lymphatic system. However, the lymphatic system has another important impact regarding the vascular refilling: acute bleeding leads to a dilution of blood and as a result to a reduction in the haematocrit. This normochromic, normocytic anaemia that has emerged is a characteristic early sign of major blood loss (1). Accompanied

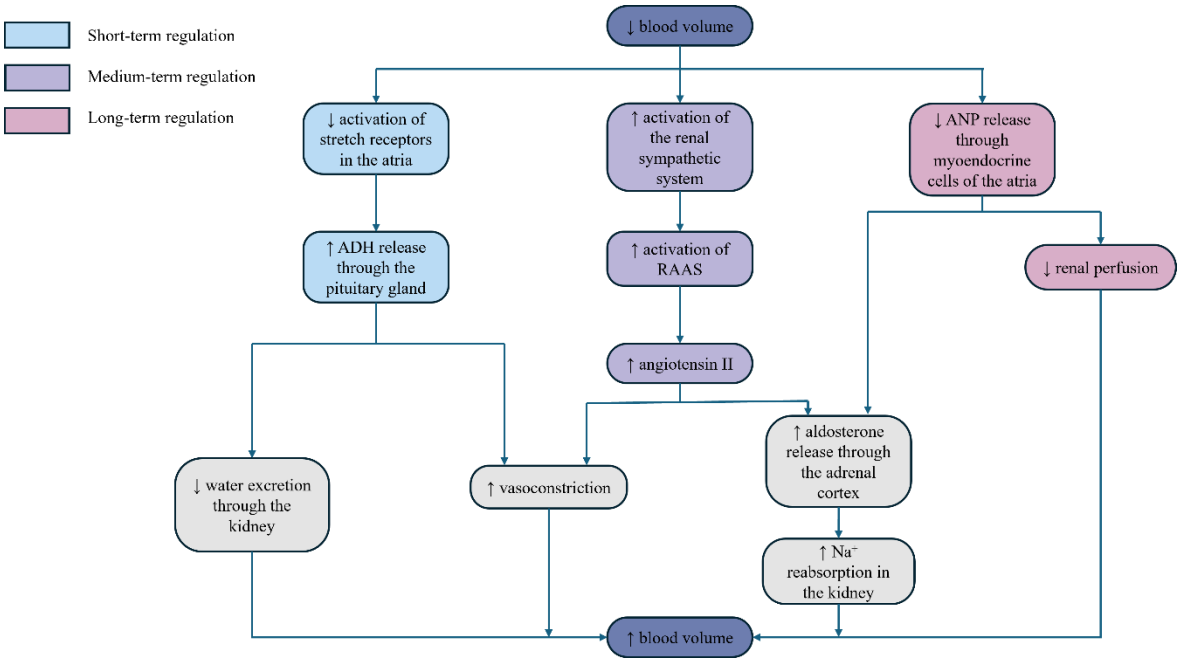
by the lymph, albumin is reintroduced into the circulatory system through the thoracic duct and helps with preventing hypovolemia. (2)

On the other hand, various hormone systems have an impact on the long-term volume regulation (see Figure 1): In case of low blood volume, the posterior lobe of the pituitary gland releases antidiuretic hormone (ADH). A high plasma concentration of ADH leads to reduced water excretion through the kidneys and therefore to an increase in blood volume. Furthermore, ADH has a constrictive effect on arterial resistance vessels and small veins. This allows the blood volume to be shifted from the periphery to the centre. (1)

The renin-angiotensin-aldosterone system (RAAS) also plays an important role in case of volume deficiency. The resulting angiotensin II has a strong vasoconstrictive effect. Additionally, it promotes the release of aldosterone from the adrenal cortex, which stimulates the Na^+ reabsorption mechanisms in the kidneys. This process affects long-term volume regulation because it helps refill the extracellular volume. (1)

Atrial natriuretic peptide (ANP) is synthesised and stored by myoendocrine cells of the atria. In case of increased extracellular volume ANP is released and inhibits the Na^+ reabsorption in the kidneys and the aldosterone release from the adrenal cortex. This leads to a reduction in the extracellular volume. Conversely, lower ANP results in an increase in volume. (1)

Figure 1: Hormonal mechanisms of blood volume regulation in case of volume deficiency. (1)



In general, a well-functioning circulatory system requires a physiological pumping function of the left ventricle as well as an adequate venous return to the heart. Three parameters are relevant for sufficient venous return: the right atrial pressure, the mean systemic pressure (PMS) and the vascular resistance. The PMS is the pressure that operates against the pressure in the right atrium to allow forward flow. It is established by the intrinsic compliance of the vascular bed and the total amount of venous blood. The vascular bed needs to be filled to a particular level in order to apply pressure on the vessel walls. This is referred to as the unstressed volume. Above this level, any volume is called the stressed volume, which exerts a much stronger pressure on the vascular bed. With increased stressed volume, both the PMS and the venous return increase. (3)

Acute blood loss causes a reduction in total volume, which lowers the stressed volume. Initially, the body tries to compensate for this loss of volume with catecholamine-induced vasoconstriction via the sympathetic nervous system (see above) (1,3). By transferring blood from the unstressed to the usable stressed volume, this compensatory mechanism raises the PMS and keeps the venous return intact. Vasopressors, such as norepinephrine, may also be used to accomplish this effect. If blood loss persists, this mechanism is no longer sufficient

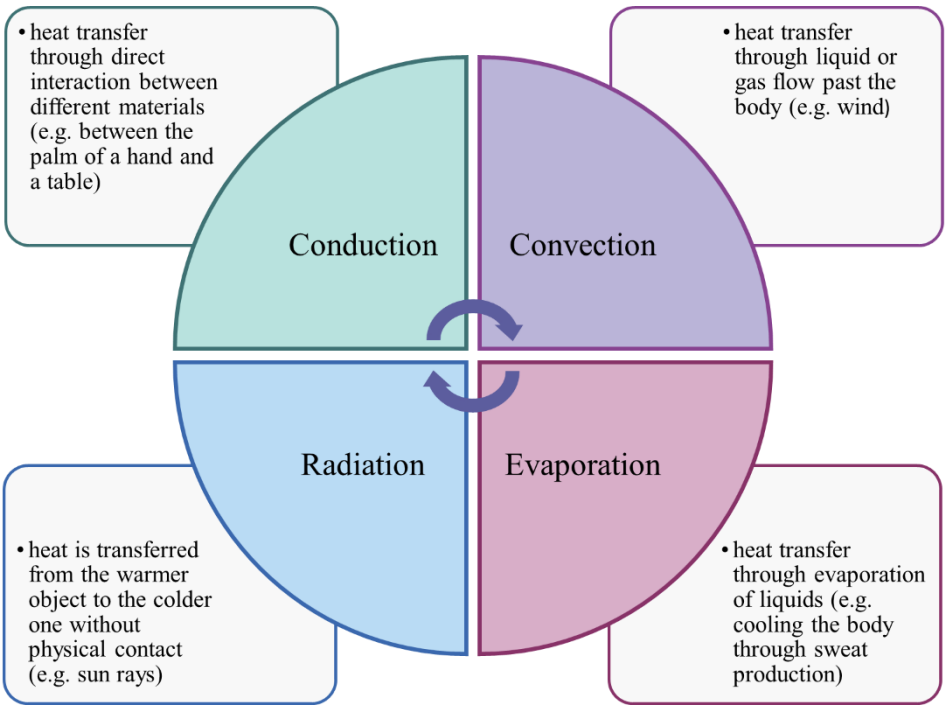
and volume replacement is required. Volume replacement increases the total blood volume and the stressed volume and therefore helps to recreate a more physiological state. (3)

7.1.2 Thermoregulation

Maintaining a constant body temperature is essential for general homeostasis. This stability is mainly important for the internal organs (body core), whereas larger temperature fluctuations can be seen in peripheral tissues (body shell). Normothermia is defined as temperatures between 36 °C and 38 °C. Throughout the day, this temperature may vary between 0.5-0.7 °C due to circadian fluctuations. (4)

The aim of thermoregulation is to maintain an ideal core temperature while managing fluctuations in heat generation and heat dissipation. Heat generation depends on the energy metabolism. Heat dissipation works by using four physical mechanisms (see Figure 2). An imbalance between these might result in hypothermia or hyperthermia. (4,5)

Figure 2: Graphic of the main physical mechanisms of heat dissipation of the human body. (4)



Free nerve endings, so-called peripheral thermosensors, are located in the skin. They are classified into cold and warm receptors, which detect the temperature of the body's surface and the rate of temperature change. This creates an early warning system that initiates prophylactic mechanisms to prevent a change in the body's core temperature. (4)

Central thermosensors are found in the spinal cord, brainstem and hypothalamus and measure the body's core temperature. The hypothalamus is the centre of temperature regulation. Its task is to compare the actual temperature with the setpoint temperature. Effector mechanisms are triggered by the hypothalamus when temperature fluctuations of ± 0.1 °C occur. (4,5)

Information from the peripheral and central thermosensors is transmitted to the dorsomedial hypothalamus through the medial preoptic region. This leads to excitation (via glutamate, when cold) or inhibition (via gamma-Aminobutyric acid (GABA), when warm) of serotonergic neurones in the brainstem. This results in altered sympathetic activity within the neurones of the lateral horn and associated effector mechanisms:

If the body temperature rises above the set point, the blood flow to the skin is increased due to vasodilation. Furthermore, there is a higher production of sweat, allowing the skin to cool down more.

If the temperature falls below the set point, the blood flow to the skin, and therefore the heat dissipation is reduced due to vasoconstriction. Heat generation now increases with the contraction of the striated skeletal muscles and muscular tremors, so-called shivering. (4)

7.2 Pathophysiology

7.2.1 Hypothermia

A core body temperature below 35 °C is defined as hypothermia. Depending on the severity and how long the hypothermia remains untreated, different physiological changes can be seen. In 1994, Danzl defined four stages of accidental hypothermia (see Figure 3). Although several other categorisations are available, this text refers to the states of hypothermia according to Danzl. (6)

Physiological functions decrease in line with the body's core temperature if the compensatory mechanisms are no longer able to keep the body in a normothermic state. This affects the organ systems in different ways:

Cardiovascular system: Once the body's core temperature falls below 36 °C, catecholamines are released by the sympathetic nervous system. This results in tachycardia, vasoconstriction and an increase in cardiac afterload, mean arterial pressure and cardiac output. Further cooling leads to a physiologic bradycardia and therefore to a linear reduction in heart rate (decrease of 50% at ~ 28 °C). Since temperature also affects membrane channels and therefore membrane currents, changes in the electrocardiogram (ECG), such as expanded QRS complex, prolonged QT interval and T-wave inversion, may be seen. When the temperature drops to 32 °C, the threshold for atrial and ventricular arrhythmias is reduced. A high risk of ventricular fibrillation (VF) and asystole occurs at temperatures below 28 °C. Cardiac output continuously decreases to 45% at ~ 25 °C due to increased afterload, decreased heart rate and decreased calcium sensitization. Vasoconstriction fails at temperatures below 24 °C, which results in a poikilothermic patient, a progressive reduction in arterial blood pressure and to low-flow organ perfusion. (7)

Central nervous system: There is an increase in cerebral metabolism at the beginning of the temperature fall. With every degree Celsius that the core temperature drops, there is a corresponding 6% decrease in oxygen demand. A decrease of only 4 °C from the normal core temperature causes a noticeable decline in cognitive function. This impairment of cerebral homeostasis caused by hypothermia is described as a transient organic brain syndrome. Behavioural

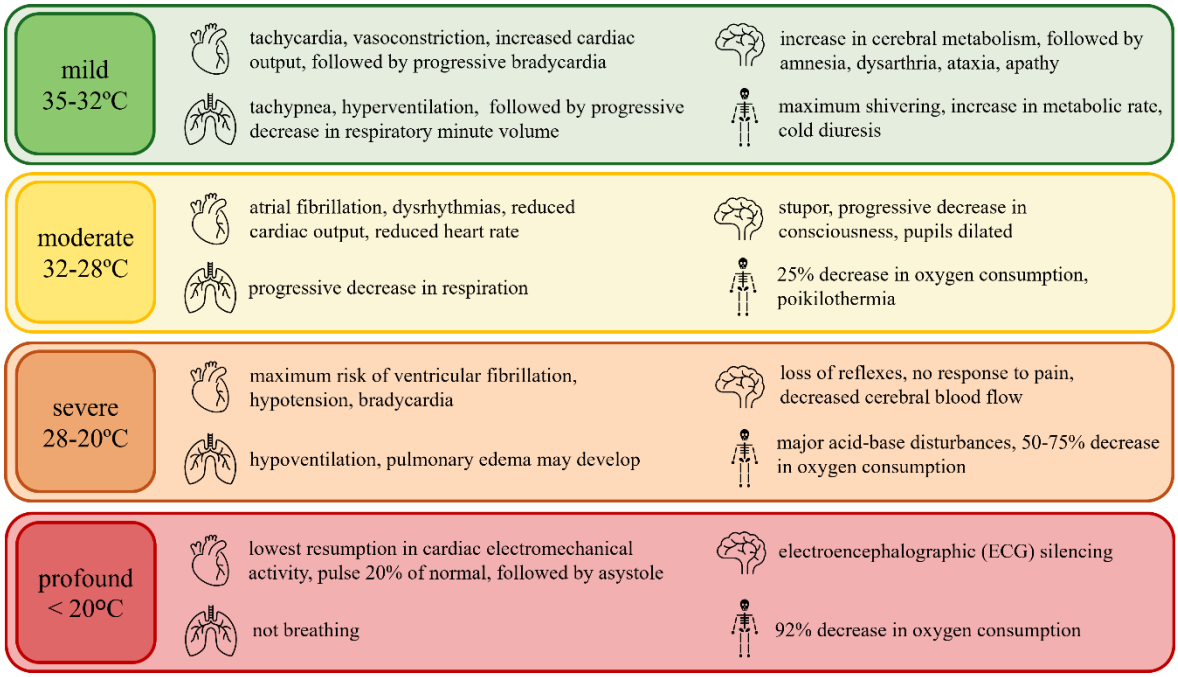
changes, disorientation, dysarthria, ataxia, amnesia, and apathy are typical symptoms. (7)

Respiratory system: When the core temperature drops between 37-35 °C, the oxygen consumption and the metabolic rate are highly increased (about +500%) due to catecholamines. During the temperature fall the initial hyperventilation is followed by a progressive decrease in tidal volume and respiratory rate, which may result in CO_2 tissue retention and respiratory acidosis. Additionally, a decrease of compliance and thoracic elasticity and an increased dead space can be seen. Furthermore, when core temperature drops, neurocontrol over breathing also declines, particularly at the brainstem level. Core temperatures below 28 °C could result in apnoea. (7)

Fluid shifts and kidney function: Due to exposure to cold, peripheral vasoconstriction sequesters plasma volume without trapping red blood cells. This leads to a fluid shift from the intracellular to the extracellular space and an increased haematocrit. As a result, there is a hypervolemia that suppresses ADH leading to what is known as “cold diuresis”. The drop in renal oxygen consumption that occurs throughout the cooling process also affects renal metabolism and tubular function, leading to a notable decline in these parameters. (7)

Blood and coagulation parameters: For every degree Celsius decrease in core temperature, blood viscosity rises by 2%, increasing haematocrit and haematologic concentration. The oxyhaemoglobin dissociation curve shifts to the left during temperature fall, exposing cells to higher levels of hypoxia. Additionally, certain enzyme functionality is decreased by hypothermia, which leads to a dissociation between homeostatic enzyme activity and clotting factor levels. This in turn may result in hypocoagulability, which can be seen by a prolongated prothrombin time and activated partial thromboplasmin time tests. However, a combination of increased viscosity, haemoconcentration and an inflammatory cascade (similar to disseminated intravascular coagulation) can also cause hypothermic patients to become hypercoagulable. In patients undergoing elective surgery, a retrospective meta-analysis showed that a drop of 1 °C in core temperature was associated with an increased risk of bleeding (+16%) and an increased need for transfusions (+22%). (7)

Figure 3: Summary of the four stages of hypothermia according to Danzl. (7)



Hypothermia is categorised not only by severity but also by duration: as acute (few hours), prolonged (several hours) or chronic (days or weeks). (6)

Additionally, a differentiation between primary and secondary hypothermia is made. Primary hypothermia is the result of an individual's heat production being overpowered by extreme cold stress. Secondary hypothermia may develop regardless of the surrounding temperature. It arises due to a wide variety of medical disorders, including hypoxia, major infections, burns, cold infusions, trauma and shock. (7)

Despite concerns about accidental hypothermia, therapeutic hypothermia shows that an organism with a lowered core body temperature is significantly less vulnerable to harmful effects of the environment compared to a body in normothermia. It shows that hypothermia allows the interruption of blood circulation for up to one hour without causing damage to the body, whereas in normothermia circulatory arrest can be tolerated for only four to five minutes. The modern cardiac surgery has benefitted significantly from the use of therapeutic hypothermia: By inducing hypothermic cardiac arrest (HCA), the heart's oxygen demand is immediately reduced by 90%. Along with that, a cardiopulmonary bypass (CPB) is

used to deliver cold, oxygenated blood to the remaining organs. This allows the surgeon to complete the heart reconstruction procedure in the most secure way. (6)

Less success has been documented with the use of therapeutic hypothermia to protect organs during neurosurgical procedures or after traumatic brain injuries. Preventing hyperthermia and maintaining a physiological body temperature appear to have the best neuroprotective effects. (6)

The therapeutic hypothermia is considered the standard procedure for the protection of donor organs from ischemia and hypoxia. However, a drop in temperature leads to an increase in blood viscosity and therefore to harmful coagulopathies in the donor organs. Therefore, in addition to hypothermia, certain preservation solutions are crucial for ensuring the greatest possible protection for donor organs. (6)

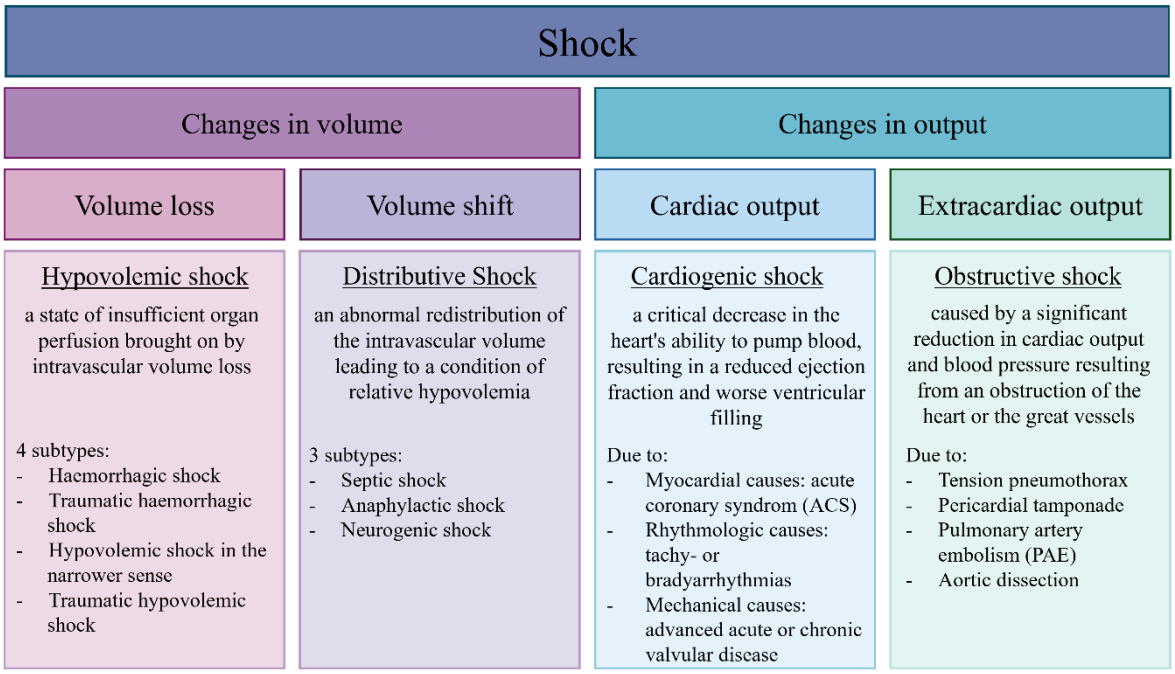
Nevertheless, throughout the past 50 years, clinical trials have not shown any beneficial advantages of induced hypothermia over maintaining normothermia in the majority of severe circumstances. (6)

7.2.2 Shock

Shock is a highly feared medical condition, with mortality rates ranging from 40-60% (8). It occurs due to an imbalance between oxygen supply and demand at the cellular level. At first, shock is a reversible condition, but it soon enters an irreversible phase that ultimately results in multiple organ failure (MOF). Based on the pathogenesis, four different types of shock are distinguished (see Figure 4). (9)

As two specific types of shock are of particular importance to this thesis, they are discussed in more detail in the following chapters.

Figure 4: Overview of the four types of shock. (10)



7.2.2.1 Hypovolemic shock

As illustrated in Figure 4, hypovolemic shock can be categorized into four subtypes:

Haemorrhagic shock is caused by an acute bleeding without significant damage to soft tissues. Clinically, a nontraumatic vascular rupture (such as an aortic aneurysm), gastrointestinal bleeding or abrupt haemorrhage from a major blood vessel are the main causes of haemorrhagic shock. (10)

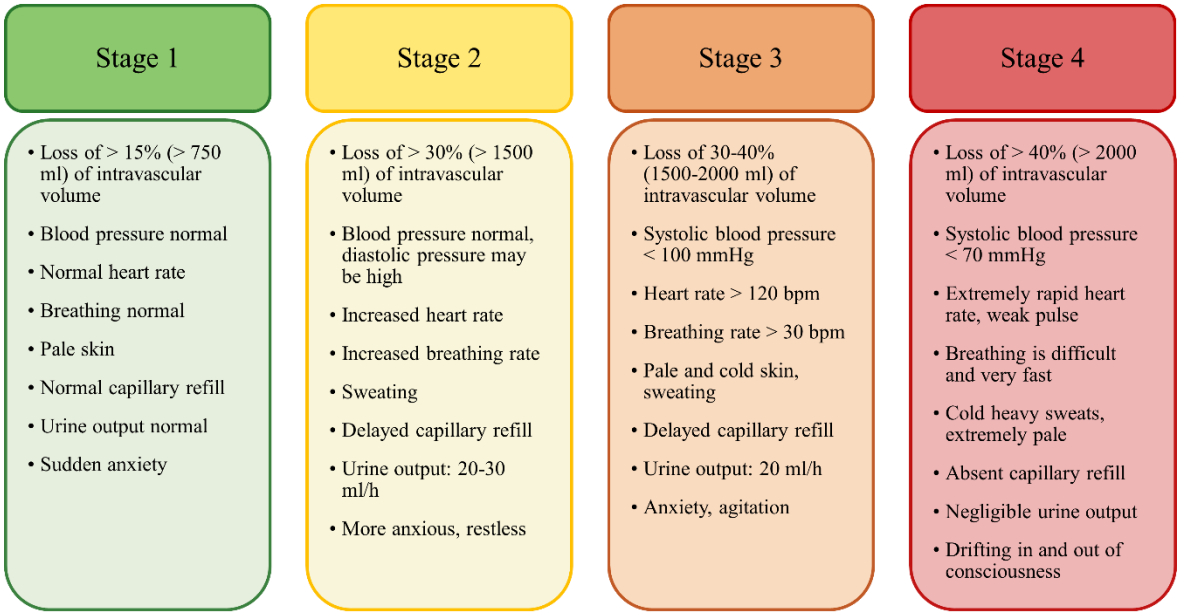
Traumatic haemorrhagic shock, in contrast to haemorrhagic shock, is accompanied by severe soft tissue damage. The injury of the soft tissue leads to post-acute inflammation, further intensifying the shock process. Polytrauma, often caused by car accidents or falls from high altitude, is a common example of this kind of shock. (10)

Internal or external fluid loss, combined with insufficient fluid intake, can lead to a **hypovolemic shock in the narrower sense**. This condition is characterised by a critical drop in plasma volume without significant bleeding. It can result from uncompensated renal losses (such as diabetes insipidus or hyperosmolar diabetic coma), hyperthermia, or chronic diarrhoea and vomiting. (10)

Massive surface burns, chemical burns and deep skin lesions are common causes of **traumatic hypovolemic shock**. Similar to the hypovolemic shock discussed above, this type also results from a severe reduction in plasma volume without acute blood loss. However, the trauma further exacerbates the impairment of both macro- and microcirculation by activating the immune system and the coagulation cascade. The inflammatory response leads to severe coagulopathy, raises the risk of capillary leak syndrome, and damages the endothelium. (10)

Based on the amount of blood loss, hypovolemic shock can be classified into four different stages (see Figure 5). (11)

Figure 5: Stages of hypovolemic shock. (11)



It has been proven that the so-called “lethal triad” of acidosis, coagulopathy and hypothermia increases the risk of morbidity and mortality in trauma patients. However, recent studies have shown that hypocalcaemia also has a significant impact on patient outcomes in haemorrhagic shock. This resulted in the concept of the “diamond of death”, a cycle consisting of four interrelated factors: acidosis, coagulopathy, hypothermia and hypocalcaemia, each potentially worsening the others. (12)

A persistent loss of volume leads to a decrease in venous return (preload) and arterial blood pressure. To prevent shock, compensatory tachycardia and vasoconstriction occur with the aid of volume regulating mechanisms (see 7.1.1 Volume regulation). (1,9)

As a result of vasoconstriction, blood flow to peripheral organs such as the skin and skeletal muscle is rapidly reduced, prioritizing vital organs like the heart and brain. The brain's autoregulation system maintains consistent cerebral blood flow despite fluctuations in mean arterial pressure (MAP). This is achieved by adjusting cerebral vascular resistance. If the amount of oxygen reaching the brain falls below the oxygen demand, proinflammatory mediators are released, which may increase the permeability of the blood-brain barrier and can lead to oedema, increased intracranial pressure and unconsciousness. (9)

With further loss of volume, the systolic blood pressure decreases and oxygen supply to the organs can no longer be maintained. As a consequence, cells switch from an aerobic to an anaerobic metabolism. This leads to the production of lactic acid and therefore to **acidosis** (pH < 7,35). (11,12)

The peripheral vasoconstriction that emerges due to the need to perfuse vital organs even exacerbates lactic acidosis because of the lack of oxygen reaching the extremities. In trauma patients, the therapy with intravenous crystalloids is used to expand intravascular volume. However, acidosis gets worse because crystalloids have a dilutional effect and are not able to transport oxygen. The resulting acidosis further impairs coagulation: due to the pH-dependence of clotting factors, acidosis reduces coagulation factor activity and leads to an increased coagulation time and reduced cloth strength. (12)

In trauma patients, the loss of clotting factors can lead to **trauma-induced coagulopathy** (TIC). TIC develops 30 minutes after trauma and leads to an abnormal activation of the clotting cascade. An imbalance between clotting, fibrinolysis and anti-coagulation may lead to excessive clot formation and clot disintegration, causing a rapid consumption of clotting factors in bleeding patients. The persistence of the bleeding, as well as the treatments given, exacerbate TIC: By using intravenous fluids, the body's natural clotting factors and the oxygenated

haemoglobin are getting diluted, further aggravating acidosis, as already mentioned above. (12)

Trauma patients often experience **hypothermia** due to environmental temperatures. But also peripheral vasoconstriction or traumatic brain injuries may have a negative effect on thermoregulation. In hypothermic patients, the clotting cascade is inappropriately activated and cannot operate as it should. Consequently, hypothermia exacerbates coagulopathy. Also, hypothermia causes the oxygen-haemoglobin dissociation curve to shift to the left, which lowers tissue oxygen and myocardial contractility, leading to an increased oxygen dept and to an exacerbation of the acidosis. (12)

Calcium is required for the conversion of prothrombin to thrombin, the activation of clotting factors, platelet adhesion and thrombus formation. Due to massive bleeding, trauma patients frequently experience hypocalcaemia (serum calcium < 8 mg/dL) leading to an exacerbation of coagulopathy and acidosis. But also the therapy with blood products may result in a drop of calcium levels: the citrate used for chelating calcium in the packed blood cells cannot be metabolized efficiently due to hypothermia and decreased liver perfusion. As a consequence, calcium is continuously removed from the circulating blood and unavailable for use, resulting in hypocalcaemia. Studies showed that trauma patients with significantly low calcium levels require more blood products for resuscitation and have an increased mortality rate compared to patients with normal calcium, further demonstrating the importance of hypocalcaemia as a component of the diamond of death. (12)

7.2.2.2 Distributive shock

Distributive shock is by far the most common form of shock, resulting from an abnormal redistribution of the total intravascular blood volume. The underlying issue is either an increased permeability of the vascular wall with intravascular volume being shifted into the interstitium, or a pathological dilatation of the blood vessels with volume shifting within the vascular system. As illustrated in Figure 4, distributive shock is classified into three subtypes, based on aetiology. (10,13)

Septic shock

Sepsis is defined as an exaggerated reaction of the body to an infection, resulting in lethal organ dysfunction. With mortality rates ranging from 35-40%, septic shock is a severe life-threatening condition (14). It is characterised by lactate levels > 2 mmol/L and persistent hypotension that demands vasopressor therapy to maintain a MAP > 65 mmHg (10).

Infections in septic patients most commonly emerge from the lungs (64%), abdomen (20%), bloodstream (15%) and urinary tract (14%) and are often caused by gram-negative bacteria, like staphylococcus aureus (14). Cells of the innate immune system are able to recognise pathogen-associated molecular patterns (PAMP), such as bacterial lipopolysaccharides. As a result, an immune response is triggered, leading to an increased release of pro-inflammatory mediators. Although these lead to a rapid improvement of a local infection, in case of a generalised reaction, as in sepsis, they may cause substantial tissue and organ damage. The vascular endothelium is particularly affected, leading to increased vascular permeability. This results in an accelerated loss of fluid into the interstitium and to a formation of interstitial oedema. Furthermore, an increased concentration of nitric oxide (NO) worsens vasodilation. (13)

Septic shock is a combined form of numerous pathologies, ultimately resulting in MOF, and is typically associated with coagulopathies (such as disseminated intravascular coagulation (DIC)), septic cardiomyopathy, acute respiratory distress syndrome (ARDS), acute kidney injury, septic encephalopathy and liver failure. (10,14)

Anaphylactic shock

Anaphylaxis is defined as an acute systemic IgE-mediated hypersensitivity reaction, triggered by the exposure to an allergen. Due to a massive release of histamine by mast cells, vasodilation occurs accompanied by a volume shift from intravascular to extravascular space, resulting in a state of anaphylactic shock. In contrast, anaphylactoid shock is independent of the antigen-antibody reaction and is typically triggered by X-ray contrast medium, dextran or nonsteroidal anti-inflammatory drugs

(NSAID) (13). In this case, histamine is released from mast cells and basophilic granulocytes due to chemical, osmotic or physical hypersensitivity reactions. (10)

The three most common triggers of anaphylactic reactions are drugs, food products and insect venoms. These reactions may be intensified by stress, physical activity and acute infections. The symptoms depend on the dose and route of exposure to the antigen, as well as the level of sensitization. Starting with abdominal symptoms, skin rashes and respiratory problems, the symptoms can rapidly extend to anaphylactic shock with a lethal outcome. In the state of shock thromboembolic events, arrhythmias and cardiovascular failure can be seen. (10)

Neurogenic shock

Neurogenic shock carries a mortality rate around 20% and occurs due to a dysregulation of cardiac action and vascular adaptation: The sympathetic nervous system induces vasoconstriction in the peripheral vascular system through the release of noradrenaline. Vasodilation, on the other hand, is triggered by reduced sympathetic activity. If the sympathetic innervation is disrupted, for example due to spinal trauma, ischaemia, brainstem trauma, drugs or in paraplegic patients (due to a breakdown of the descending pathway from the bulbar regulatory centres to the spinal cord), acute inadequate vasodilation and bradycardia occurs. (10,13)

Sudden vasodilation with associated relative hypovolemia, bradycardia and hypotension, as well as unconsciousness and a loss of spinal reflexes (in case of high spinal cord injury) are the main symptoms of neurogenic shock. (10)

7.2.3 Volume replacement therapy

As demonstrated in the previous chapters, hypovolemia is a crucial component of all forms of shock. Whether the hypovolemia is relative (distributive shock) or absolute (hypovolemic shock), rapid fluid resuscitation is usually required. An optimal resuscitation fluid should enhance microvascular blood flow and restore cardiac and intravascular filling without harming endothelial integrity or causing capillary permeability. Inadequate fluid administration may lead to hypervolemia, resulting in increased fluid extravasation, ultimately causing pulmonary oedema or acute kidney injury. This emphasises the importance of choosing the right amount

of volume substitution individually for every patient and type of shock. Depending on the underlying pathology, options for fluid administration may include erythrocyte concentrates like packed red blood cells (PRBC), plasma products like fresh frozen plasma (FFP), colloid solutions or crystalloid fluids. A short overview is presented in Figure 6. (15)

Table 1: Types of Volume resuscitation (10,15)

Volume resuscitation	Indication	Effect	Risks
Cristalloid solutions	All forms of shock with reduced cardiac preload	Rapid restoration of intravascular volume, increases cardiac preload	Hypervolemia, tissue edema
Modern semisynthetic colloids (hydroxyethyl starch (HES), gelatines)	Short-term stabilization of hypovolemia when crystalloids are insufficient	Longer intravascular persistence compared to crystalloids, lower infusion volume required	High risk of acute kidney injury (AKI), coagulation disorders, potential anaphylactic reactions
Albumin	Hypoproteinemia, severe sepsis, or marked hypovolemia	Raises colloid osmotic pressure, may improve microcirculation	Increased risk of AKI due to hyperoncotis perparations, higher rates of bleeding and death in haemorrhagic shock
Erythrocyte concentrates	Anaemia with haemodynamic instability, acute haemorrhage	Red blood cells replacement, improves blood coagulability, increases oxygen-carrying capacity	Transfusion reactions, risk of infection, hyperkalemia
Fresh frozen plasma (FFP)	Coagulopathy with bleeding tendency, e.g., during massive transfusion	Supplies clotting factors and plasma proteins, good effect on volume expansion and extended intravascular stay	Risk of allergic reactions, infection, acute transfusion reaction, volume overload
Platelet concentrates (PC)	Thrombocytopenia or platelet dysfunction with bleeding risk	Improves primary haemostasis by replacing platelets	Immune reactions, infection
Coagulation factors	Specific coagulation factor deficiencies (e.g., haemophilia), massive bleeding with factor depletion	Direct replacement of the deficient factor, after loss or after the use of vitamin K inhibitors or New oral anticoagulants (NOAC)	Thrombosis risk, possible allergic reactions

7.3 Rapid Infusion Systems

In case of major blood loss, volume replacement agents are often administered at high flow rates to restore normovolemia. However, high transfusion rates may not allow sufficient warming of the transfusate, which can be particularly problematic if unheated red blood cell concentrates are used. This could result in a hypothermic patient with the associated consequences (see 7.2.1 Hypothermia). Rapid Infusion Systems (RIS) are designed to provide high flow rates while ensuring effective heating in order to achieve both normovolemia and normothermia. They therefore play an important role in situations where aggressive volume therapy is necessary. (16,17)

The most important indications for the use of RIS are presented below.

7.3.1 Indication

7.3.1.1 Traumatic and non-traumatic haemorrhage

Major blood loss is one of the leading causes of death among trauma patients (18). However, non-traumatic bleeding – such as oesophageal variceal bleeding, diverticular bleeding, uterine haemorrhage, or a ruptured aortic aneurysm – may also result in massive blood loss with potentially severe consequences (9).

Along with tranexamic acid and rapid haemostasis, volume replacement is the preferred treatment in preclinical trauma patients. The volume substitution of choice involves early transfusion of blood components combined with limited crystalloid administration. However, recent studies have shown that a generous administration of crystalloids should be avoided – excessive fluid or blood may raise MAP but can also lead to a reduced peripheral vasoconstriction, further increasing haemorrhage, and causing hydrostatic injury to already damaged vessels. Therefore, the so-called permissive hypotension occurs: by tolerating a blood pressure below the physiological level, an adequate vascular tone is preserved, the sufficient perfusion of vital organs is ensured, and the risk of coagulopathy is reduced. The permissive hypotension approach should not be used in patients with traumatic brain injury (TBI), as they require a higher blood pressure (systolic blood pressure (SBP) > 110 mmHg) to maintain cerebral perfusion pressure (CPP). (16,19)

In patients without TBI it is recommended to start volume resuscitation at a MAP of 50 mmHg with fluid boluses ranging from 100 to 200 ml, while MAP responses are being evaluated. (16)

Mild hypothermia in trauma patients is associated with poorer prognosis and with a raised need for fluids and blood products. Therefore, it is crucial to prevent initially normothermic trauma patients from developing hypothermia. According to Advanced Trauma Life Support (ATLS) recommendations, blood or crystalloids should be heated up to 39 °C prior to infusion, particularly in cold conditions. (16)

Rapid bleeding control and adequate, warmed volume substitution are essential to prevent patients from spiralling into the diamond of death, ultimately resulting in an irreversible state of shock (see 7.2.2.1 Hypovolemic shock). (12,18)

RIS allow rapid and controlled intravenous fluid administration while protecting the patient from hypothermia by warming the fluid prior to injection. Therefore, they are commonly used in these patient groups and serve as preferred strategy for the treatment of patients in shock. (20)

7.3.1.2 Burns

Severe burns cause significant fluid loss through the affected skin areas, leading to rapid fluid accumulation in the damaged tissue and thus to an intravascular volume deficiency. Burns involving 15-20% of the total body surface area (TBSA) may result in hypovolemic shock, organ failure and eventually death if adequate volume replacement is not provided. For this reason, appropriate fluid substitution is one of the most important therapeutic approaches in burn victims. Commonly, the modified Parkland formula is used to calculate each patient's individual fluid needs over 24 hours, estimating it with 2 mL/kg/% TBSA. Although advanced haemodynamic monitoring devices exist to enhance fluid administration in this critical condition, like Pulse index Continuous Cardiac Output (PiCCO) measurement, the formula remains in use when these devices are unavailable. Within the first eight hours, half of the predicted volume should be provided. To ensure that the correct amount has been administered, urine output can be used as an indicator. (21)

7.3.1.3 Post-reperfusion syndrome (PRS)

When tissue hypoxia or ischaemia occurs – for example after myocardial infarction, traumatic limb injury, organ laceration or during organ transplantation – it may cause damage at the cellular level. The required therapeutic revascularisation can lead to what is known as ischaemic reperfusion injury (IRI): the sudden rise in blood and oxygen supply due to revascularisation triggers the production and release of oxygen radicals and inflammatory cells into the circulation, causing cytokine release and further damage at the cellular level. (22,23)

The released proinflammatory cytokines, such as Tumor necrosis factor alpha (TNF-α), Interleukin-1 beta (IL-1β) and Interleukin 6 (IL-6), lead to increased NO production and consequently to vasodilation and increased vascular permeability resulting in hypotension and hypovolemia. (24,25)

IRI can subsequently lead to the so-called post-reperfusion syndrome (PRS), a serious complication that may occur, for example, in cardiac arrest, acute limb ischaemia, during cardiac surgeries or liver transplantation. (23,26)

As the pathophysiology of PRS can be clearly illustrated in the context of liver transplantation, it will be discussed in more detail below.

PRS is a potentially severe complication that may arise during liver transplantation. The procedure is performed in three surgical steps: hepatic resection (mobilisation of the liver), anhepatic phase (removal of the liver, preparation for the donor organ) and neohepatic phase (donor liver starts its function). (23,27)

Severe haemodynamic changes can be frequently seen in the neohepatic phase: By opening the portal vein clamp, blood flow is reestablished through the graft. When acute hypotension, arrhythmia or, in the worst case, cardiac arrest occur after this step, it is referred to as PRS. (23)

The pathomechanism of PRS is not yet entirely understood. However, it is assumed that the haemodynamic abnormalities are caused by a massive flow of cold, acidotic blood to the heart after the reopening of the portal vein. The interruption of the blood supply to the liver during transplantation may lead to IRI, which damages the liver cells and triggers the production and release of oxygen radicals and inflammatory cells into the circulation, further aggravating hypotension. (23)

Careful perioperative monitoring of arterial blood pressure in combination with transesophageal echocardiography (TEE) allows accurate fluid administration and therefore reduces the risk of developing PRS. (23)

7.3.2 How RIS work: Different Heating and Pressure Mechanisms

Four commonly used rapid transfusion systems on the European market are the **AutoMer II** (Ace Medical, Seoul, Republic of Korea), the **Belmont® Rapid Infuser RI-2** (Belmont Medical Technologies, Billerica, MA, USA), the **Fluido® Airguard (**TSC Life, Amsterdam, The Netherlands) and the **3M™ Ranger™** (Solventum Corporation, Maplewood, MN, USA). Since the functional mechanisms of the devices vary by manufacturer, the following chapter provides a brief overview of the different heating and pressure mechanisms of each device.

7.3.2.1 Heating technology

RIS like the **AutoMer II** or the **3M™ Ranger™** typically use dry heat technology for fluid warming. The solution passes through a sterile disposable cassette which is in direct contact with electrically heated aluminium plates. The generated heat is transferred through these contact surfaces, consequently leading to the warming of the fluid. (28,29)

The **Fluido® Airguard** combines dry heat with infrared technology. Infrared radiation is used to warm the heating plates, which then transfer the generated heat to the cassette and ultimately to the fluid. (30)

The **Belmont® Rapid Infuser RI-2** uses a heating method which differs from the dry heat systems mentioned above: The fluid runs through a sterile disposable cassette which is connected to a metallic heat exchanger. Using induction, a coil generates an electromagnetic field that heats the heat exchanger quickly and evenly. The generated heat is transmitted straight to the fluid without it being in direct contact with the heating element. (31,32)

7.3.2.2 Pressure mechanism

The **AutoMer II**, the **Fluido® Airguard System** and the **3M™ Ranger™** all use pressure chambers to generate pressure. This overpressure mechanically compresses the fluid bag, enabling rapid and consistent flow of the fluid into the infusion line. All devices are provided with safety features, such as pressure limitation and air detection, to minimise the risk of air embolisms and overpressure. (28–30)

In contrast, the **Belmont® Rapid Infuser RI-2** works with active pressure regulation within the infusion line: the device continuously monitors the pressure in the infusion line and regulates it automatically to ensure a safe and consistent infusion rate. If the pressure exceeds a preset limit, the infuser immediately adjusts the flow rate to prevent tissue damage and air embolisms. (31)

Table 2: Overview RIS (33)

	AutoMer II (Ace Medical Co.)	Belmont® Rapid Infuser RI-2	Fluido® AirGuard (TSC Life)	3M™ Ranger™ (3M)
Preset Temperature	41 °C	38 °C	37 °C	41 °C
Maximum Flow Rate	500 mL/min (30.000 mL/h)	1.000 mL/min (60.000 mL/h)	800 mL/min (48.000 mL/h)	500 mL/min (30.000 mL/h)
Pressurisation	Adjustable between 0–400 mmHg	Adjustable pressure limit	Adjustable between 0–300 mmHg	Adjustable between 0–300 mmHg
Pressure mechanism	Mechanically pressurised chambers	Active pressure regulation within the infusion line	Mechanically pressurised chambers	Mechanically pressurised chambers
Heating Technology	Dry heat technology using electrically heated aluminium plates	Inductive dry-heating technology using electromagnetic fields	Combination of dry heat and infrared technology	Dry heat technology using electrically heated aluminium plates

8 Material and Methods

This study examined the performance of four commonly used RIS in terms of heating cold saline and erythrocyte concentrates under high-flow conditions. It was a controlled, comparative, in vitro study conducted under laboratory conditions at the Technical Testing Centre of the University Hospital Graz, Austria.

8.1. Equipment

Temperature measurements were carried out using a **Fluke 54II thermometer** (Fluke Corporation, Everett, WA, United States of America), which has a laboratory accuracy of 0.05% + 0.3 °C and was calibrated on 26/07/2023 (Serial number 58840501WS) (34).

As already presented in Table 2, the following RIS were examined with their corresponding attributes:

- **AutoMer II, Ace Medical Co.**: Specifications for AutoPC II double chamber and AutoMer II with High Flow Set
- **The Belmont® Rapid Infuser RI-2**: Specifications for the 1000 ml/min flow rate device
- **Fluido® AirGuard, TSC Life**: Specifications for the Fluido Trauma Set
- **3M™ Ranger™, 3M**: Specifications for high flow rate sets

In this study, a sterile isotonic saline solution without preservatives was used, containing 9 g/L sodium chloride in water for injections, which was provided by Fresenius Kabi AG (Bad Homburg vor Höhe, Germany).

The local blood bank provided the erythrocyte concentrates, which were decommissioned units that had never been warmed before. This setup provided realistic conditions and made it possible to test the blood products at the highest possible flow rates.

8.2 Procedure with fluids

Prior to testing, two one-litre bags of saline solution were cooled to 4 °C using a refrigerator. Their temperatures were subsequently checked and documented to ensure they did not exceed 6 °C.

Initially, each device was tested, and the flow rate was checked. A graduated cylinder versus time measurement was used to confirm that the flow rates were comparable to the pressure bag systems. All devices were adjusted to target a flow rate of 500 mL/min.

Three of the four devices were provided with only roller clamps, which complicated accurate adjustments, frequently leading to imprecise and difficult-to-reproduce flow rates.

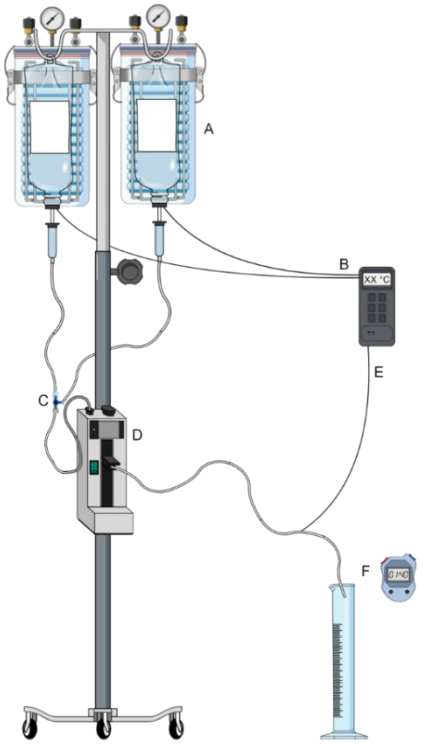
All devices were primed and set to the standard temperature. The temperature of the fluid was measured immediately before and after warming using a calibrated digital thermometer as described. To precisely simulate clinical settings, the measurement point was right before potential patient access. Once the temperature of two 1000 mL bags of physiological saline solution had been measured, the bags were clamped in place and pressure was applied in the pressurised chambers. When the clamp of the first fluid bag was opened, the time measurement started, and the temperature trend was tracked. After 1 minute and 50 seconds, the first bag was clamped, and the second bag was opened simultaneously. At 2 minutes (10 seconds later), the exact fluid volume administered for 1 minute was measured to determine the flow rate. This procedure ensured that all devices achieved optimal flow rates. After the second bag was fully emptied, the measurement had been completed. The administered volume was then measured.

The initial and final temperatures, warming time, and device-specific observations were carefully recorded. To provide an accurate representation of the environmental conditions during the test, the room temperature was noted as well at the beginning and end of the experiment.

8.3 Procedure with erythrocyte concentrates

After measuring the temperature of two erythrocyte concentrates, the units were placed into the saline-primed devices following the same protocol as used for the saline solution. For every test run, two erythrocyte concentrates were used, each containing approximately 250 mL of blood.

Figure 6: Schematic view of the experimental setup (33)



A: The pressurized chambers are adjusted to a standard pressure of 300 mmHg, suitable for the tested device. B: The temperature of each fluid or blood bag is checked immediately after it is removed from the refrigerator and before being positioned in the pressure chambers. C: Using a three-way valve the pressurized fluid can be switched between the bags. D: Fluid warming device E: Measurement of the temperature prior to possible fluid administration through the patient connector F: Assessment of the flow rate and the duration for every experimental process
Graphical design with mindthegap.com (33)

If necessary, the roller clamps were opened to the maximum, and a target flow rate of 500 mL/min was set for adjustable systems. Same as with the fluids, all erythrocyte concentrates were administered under pressure. To detect the rate of haemolysis – a possible risk for pressurized and heated transfusion units – we also

took blood samples from the bags before and after warming. Once again, the flow and temperature of the two erythrocyte concentrates were measured for each run using a pre-set saline flow of approximately 500 mL/min.

The experiment was repeated twice for each device. Due to the limited supply of blood products, no further tests were possible.

8.4 Haemolysis assessment

The haemolysis rate is a recognised parameter for tracking storage lesions in erythrocyte concentrates. For transfused patients, excessive haemolysis can have serious consequences, including increased potassium levels and free haemoglobin. Rapid heating of erythrocyte concentrates from 4 °C to 37 °C within seconds may induce haemolysis.

In this small series, the four devices were tested for haemolysis rates before and after warming. A blood count was taken on the **ADVIA 2120i blood count machine** (Siemens Healthineers International AG, Zurich, Switzerland). The blood samples were centrifuged, and free haemoglobin (Hb) in the supernatant was quantified photometrically.

Based on values from the blood count (haematocrit [HCT] and HB) and the photometric measurements, the haemolysis rate (HR) was calculated using the following formula:

$$HR = \frac{(100 - Hct) \times (HB\ from\ the\ supernatant\ [mg/dl])}{(Hb\ [g/dl]/1000)}$$

8.5 Data analysis

Descriptive statistics summarised the data, while differences in performance between the four devices were assessed using a Kruskal-Wallis test. In case of a significant difference, individual testing between the devices were carried out using Dunn's post hoc test. Data evaluation was performed by study members who were not involved in the measurement phase. This assessment blinding reduced the risk of confirmation bias. The global significance level was 0.05; a Bonferroni adjustment for multiple testing was applied.

8.6 Ethical considerations

Approval for this study was requested from the local ethics committee (Ethical Committee of the Medical University of Graz, Austria, IRB00002556 (Number 1140/2024)). All procedures followed the guidelines for safe laboratory practices.

9 Results

9.1 Primary outcome

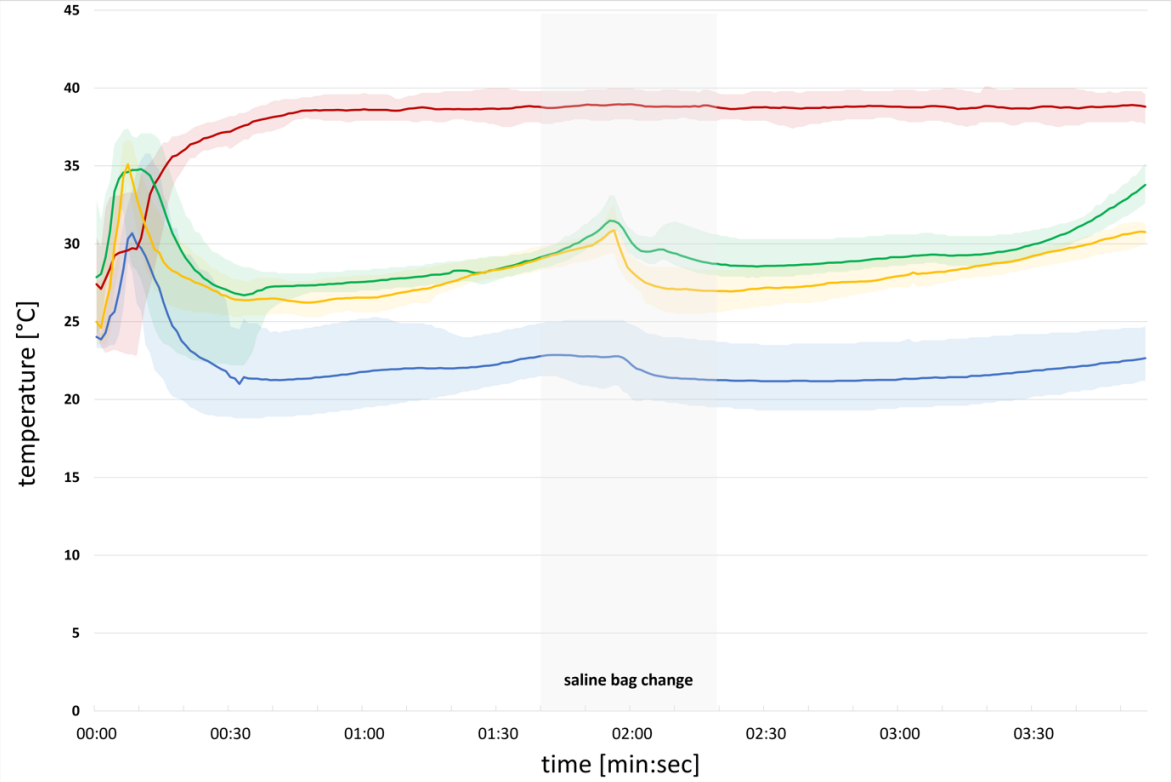
The primary outcome was the mean temperature calculated during a four-minute testing period for each RIS heating a 4-6 °C cold saline solution at high-flow conditions. Table 3 shows the baseline fluid temperatures and the flow rates achieved.

Table 3: Baseline temperatures and achieved flow rates of the test setup using saline solution. (33)

Room temperature during the testing period [°C]	22.5			
	AutoMer II (Ace Medical Co.)	**The Belmont® Rapid Infuser RI-2**	**Fluido® AirGuard (TSC Life)**	**3M™ Ranger™ (3M)**
Test 1				
baseline temperature saline bag 1 / 2 [°C]	4.9 / 5.0	5.1 / 4.5	4.2 / 4.8	4.0 / 4.7
flow rate saline bag 1/2 [ml/min]	500	530	460	460
Test 2				
baseline temperature saline bag 1/2 [°C]	5.6 / 4.8	5.2 / 4.9	5.1 / 5.0	4.6 / 4.6
flow rate saline bag 1/2 [ml/min]	490	530	500	590
Test 3				
baseline temperature saline bag 1/2 [°C]	4.1 / 4.9	5.5 / 4.0	4.7 / 5.1	5.6 / 5.9
flow rate saline bag 1/2 [ml/min]	490	520	510	570
Test 4				
baseline temperature saline bag 1/2 [°C]	4.2 / 5.4	4.0 / 4.0	4.8 / 4.6	5.5 / 4.3
flow rate saline bag 1/2 [ml/min]	350	490	510	460
Test 5				
baseline temperature saline bag 1/2 [°C]	5.5 / 4.8	4.8 / 4.7	5.0 / 4.9	4.7 / 4.4
flow rate saline bag 1/2 [ml/min]	330	460	510	500
Mean flow rate (n=5) [ml/min]	**432**	**506**	**498**	**516**

Fluid temperature measurements were taken in one-second intervals over the first four minutes and are presented in Figure 7 for each device. Median mean temperatures during the warming period were 20.8 (IQR (interquartile range): 20.5-24.8) °C for the **AutoMer II**, 37.9 (IQR: 37.7-38.0) °C for the **Belmont®**, 29.0 (IQR: 28.7-29.1) °C for the **Fluido®** and 27.7 (IQR: 27.6-27.8) °C for the **Ranger™**.

Figure 7: Mean temperatures of the saline solution achieved by the four RIS observed, measured at one-second intervals during the four-minute testing phase. Red: The Belmont® Rapid Infuser RI-2; Green: 3M™ Ranger™, 3M; Yellow: Fluido® AirGuard, TSC Life; Blue: AutoMer II, Ace Medical Co. (33)



As illustrated in Figure 8, the Kruskal-Wallis test revealed a significant difference between the devices ($p < 0.001$).

Dunn's post hoc tests with Bonferroni correction were performed on each pair of devices (see Table 4), showing a significant difference between the **AutoMer II** and the **Belmont®** ($p < 0.001$).

Figure 8: Kruskal-Wallis test results showing significant differences between the performance of the devices. Red: The Belmont® Rapid Infuser RI-2; Green: 3M™ Ranger™, 3M; Yellow: Fluido® AirGuard, TSC Life; Blue: AutoMer II, Ace Medical Co. (33)

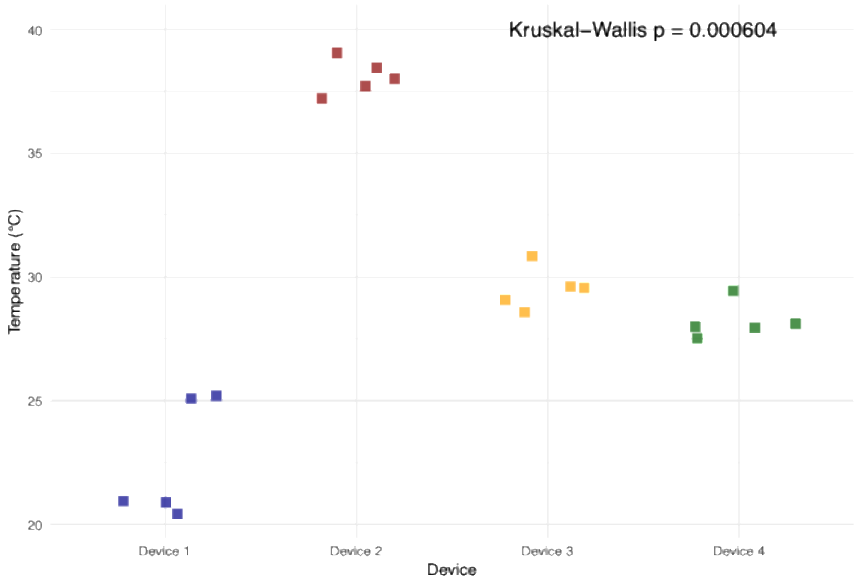


Table 4: Comparison of each pair of devices (Dunn's Post hoc tests with Bonferroni adjusted p-Value). Device 1: AutoMer II, Ace Medical Co.; Device 2: The Belmont® Rapid Infuser RI-2; Device 3: Fluido® AirGuard, TSC Life; Device 4: 3M™ Ranger™, 3M (33)

Devices	p-Value (mean temperature)
Device 1 - 2	<0.001
Device 1 - 3	0.072
Device 1 - 4	0.807
Device 2 - 3	0.807
Device 2 - 4	0.072
Device 3 - 4	1.000

9.2 Secondary outcome

The secondary outcome was the mean temperature measured during the one-minute testing period for each RIS warming erythrocyte concentrates at 4-6 °C under high-flow conditions. Table 5 presents the achieved flow rates of the different RIS and the pre-warming temperatures of the erythrocyte concentrates used in the test runs; one temperature exceeded the predefined range of 4-6 °C. (33)

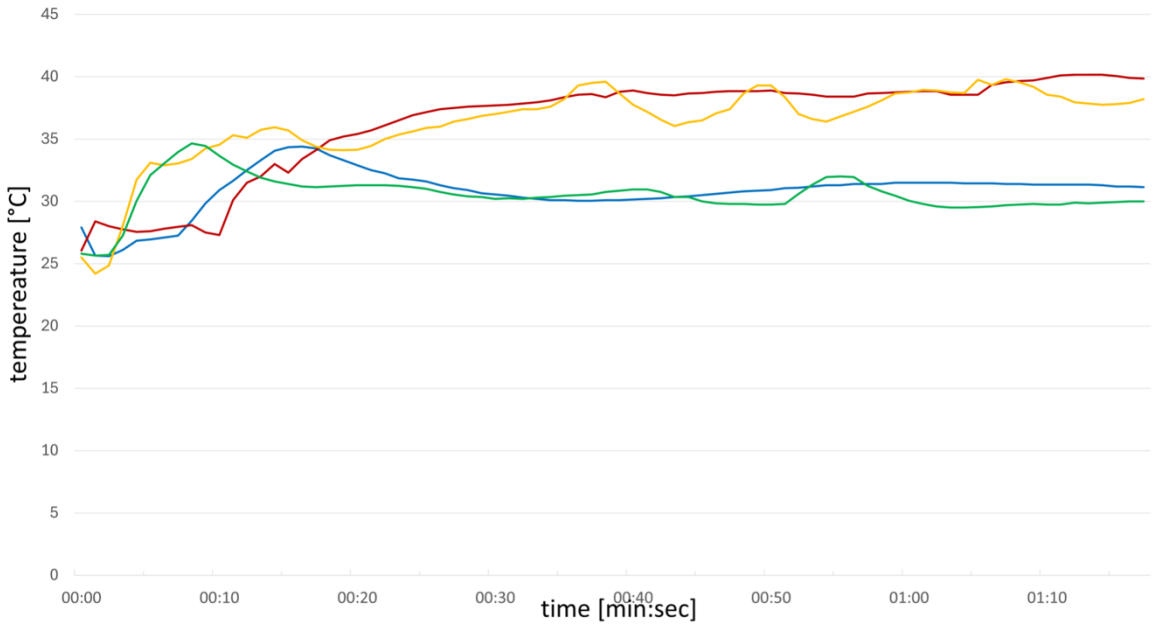
Due to the limited availability of erythrocyte concentrates, only two test runs per device were performed. Therefore, no inferential statistical analysis was conducted. (33)

Table 5: Baseline temperatures and achieved flow rates of the test setup using erythrocyte concentrates. (33)

	AutoMer II (Ace Medical Co.)	The Belmont® Rapid Infuser RI-2	Fluido® AirGuard (TSC Life)	3M™ Ranger™ (3M)
Erythrocyte concentrates test run 1				
Erythrocyte concentrate 1 [°C]	4.9	4.6	4.8	4.9
Erythrocyte concentrate 2 [°C]	4.9	4.5	4.3	4.3
Erythrocyte concentrates test run 2				
Erythrocyte concentrate 1 [°C]	5.0	5.9	4.0	5.6
Erythrocyte concentrate 2 [°C]	5.3	5.6	4.8	10.5
Achieved flow rates [mL/min]	180	480	290	395

The mean (standard deviation [SD]) temperatures of erythrocyte concentrates measured during the one-minute testing period were 30.7 (2.5) °C for the **AutoMer II**, 35.5 (4.5) °C for the **Belmont®**, 35.7 (4.2) °C for the **Fluido®** and 30.8 (2.2) °C for the **Ranger™** and are illustrated in Figure 9. (33)

Figure 9: Mean temperatures of the erythrocyte concentrates achieved by the four RIS observed, measured at one-second intervals during the one-minute testing period. Red: The Belmont® Rapid Infuser RI-2; Green: 3M™ Ranger™, 3M; Yellow: Fluido® AirGuard, TSC Life; Blue: AutoMer II, Ace Medical Co. (33)



9.3 Exploratory outcome

The haemolysis rates associated with the warming and administration of erythrocyte concentrates using RIS will be reported as an exploratory outcome.

Due to the limited availability of erythrocyte concentrates, no statistical analysis could be performed. However, mean haemolysis values before and after warming for each device are presented in Table 6.

As only expired erythrocyte concentrates exceeding their 42-day shelf life were used, the absolute haemolysis rates are not representative and are therefore not reported. However, another study demonstrated that rewarming erythrocyte concentrates within their shelf life does not increase the haemolysis rate (35).

Table 6: Mean haemolysis values of the erythrocyte concentrates using the tested devices, both pre-warming and post-warming.

Device name	Test phase	Free haemoglobin	Hb (g/dL)	HKT (%)	Haemolysis rate (%)
AutoMer II (Ace Medical Co.)	Before warming	174.50	17.225	59.3	0.416
	After warming	215.40	17.95	61.6	0.478
Belmont® Rapid Infuser RI-2	Before warming	338.30	8.125	27.275	3.179
	After warming	1072.01	16.45	55.575	2.661
Fluido® AirGuard (TSC Life)	Before warming	149.02	15.425	53.0	0.502
	After warming	519.44	17.7	60.9	1.162
3M™ Ranger™ (3M)	Before warming	825.22	16.025	50.775	2.557
	After warming	1103.04	19.475	62.35	2.169

10 Discussion

This laboratory study evaluated the heating performance of four different RIS under high flow conditions.

Among the devices tested, only the Belmont® was able to provide an output temperature close to physiological body temperature while administering two litres of 4-6 °C cold saline solution. On average, stable values around 37.9 °C were achieved. In contrast, the Fluido® reached an average outflow temperature of 29 °C, the Ranger™ about 27.7 °C. The AutoMer II was only able to heat the fluid to 20 °C. (33)

Across the five test runs using cold saline, almost all devices reached infusion volumes close to the target flow rate of 500 mL/min. The most precise flow rates were attained by the Belmont® (mean flow of 506 mL/min) and the Fluido® (mean flow of 498 mL/min). The lowest volume was administered by the AutoMer II with around 432 mL/min. The Ranger™ delivered slightly higher flow rates with an average of 516 mL/min. (33)

In the test runs with erythrocyte concentrates, the AutoMer II, the Fluido® and the Ranger™ performed markedly better in terms of output temperature compared to their performance with saline. The highest temperatures were reached by the Fluido® (mean 35.7 °C) and the Belmont® (mean 35.5 °C), with the Belmont® showing a more stable temperature curve (see Figure 9). (33)

There were significant differences in flow rates during the administration of erythrocyte concentrates: Only the Belmont® came close to the target flow rate (500 ml/min) with an average of 480 mL/min. The Ranger™ delivered 395 mL/min, the Fluido® 290 mL/min and the AutoMer II only 180 mL/min. (33)

The higher output temperatures measured during the tests with erythrocyte concentrates, along with the significantly lower flow rates, can be explained by the higher viscosity of the administered fluid: According to Poiseuille's law, the flow velocity within a vessel depends, among other factors, on the viscosity of the fluid passing through. Isotonic saline solution has a much lower viscosity than red blood cell concentrates and can therefore be infused with less resistance and thus more quickly. (36)

Red blood cells tend to aggregate, particularly at low flow rates. The resulting rouleaux may cause local perfusion deficits, especially within small blood vessels, leading to reduced tissue perfusion. These erythrocyte aggregates increase blood viscosity, resulting in higher flow resistance and consequently reduced flow rates. (37)

Furthermore, blood viscosity increases by approximately 2% for every degree Celsius decrease in body temperature (7). Therefore, the colder the infused blood, the higher its viscosity, which may reduce the achievable flow rate.

A previous study demonstrated that, due to the generally lower flow rates of the packed red blood cells, higher outlet temperatures can be achieved compared to saline solutions. The slower flow allows for longer contact times with the heating elements of the RIS, enabling prolonged heat transfer. It can therefore be assumed that higher output temperatures can be achieved at lower flow rates. In contrast, with less viscous fluids, such as saline, lower output temperatures are possible at high-flow rates due to shorter contact times with the heating elements. (38)

As already mentioned, only the Belmont® was able to come close to the target flow rate when administering erythrocyte concentrates. The Belmont® uses a peristaltic roller pump to generate pressure and create active flow through the infusion line, in contrast to the other devices tested, which use pressurisable infusion chambers (see 7.3.2.2. Pressure mechanism). (28–31,33)

It can therefore be assumed that administering a viscous fluid through a catheter system under high pressure conditions is less effective than using active pressure regulation within the infusion line, as is the case with the Belmont®. (33)

Additionally, it should be noted that the flow rate also depends significantly on the chosen size and location (central/peripheral) of the intravenous access. Our study tested the devices only up to the end of the infusion line. Therefore, no intravenous cannulas were attached at the end of the infusion set. Depending on the size of the venous access selected, this may also have a negative impact on the flow rates achieved by the tested devices. (33)

In 2019 a study compared the heat capacity of the **3M™ Ranger™ warmer** and the **FT2800 fluid warmer** at three different room temperatures (20 °C, 22 °C and 24 °C) and infusion rates between 60-350 drops/min (20 drops = 1 ml, 1 drop/min = 3 ml/h), corresponding to infusion rates between 3-17.5 mL/min. The Ranger™ is using a dry heat technology while the FT2800 fluid warmer uses a coaxial warming system for heating. Using 0.9% saline solution at room temperature, the Ranger™ produced higher output temperatures at increased flow rates, being more efficient at elevated infusion rates compared to the FT2800, which shows reduced output temperatures under the same conditions. The study also revealed that the FT2800 may reach critical temperatures above 41.5 °C at low flow rates (≤ 100 drops/min). Guidelines advise that the output temperature should not exceed 37 °C (39). Therefore, in medical fields where low infusion rates are necessary, such as paediatrics, the use of the FT2800 should be avoided due to safety reasons. (40)

Another study also examined the heat capacity of the following four RIS: the **Bair Hugger** (Bair Hugger 241 Blood ⁄ Fluid Warming Set, Augustine Medical, Eden Prairie, MN), the **Standard Ranger** (Ranger Blood/Fluid Warming System, Augustine Medical), the **Hotline** (Hotline Warming System, Graseby Medical, Watford, Herts, UK) and the **Fluido** (Datex-Ohmeda, Hatfield, Herts, UK). However, the devices were not tested under high-flow conditions, but only at a flow rate below the limit specified by the manufacturer. Within this limit, the fluid is supposed to be heated to body temperature. Furthermore, even in this study, the 0.9% saline solution was injected at room temperature, and no erythrocyte concentrates were used for testing. None of the devices tested reached the 37 °C promised by the manufacturer under the specified flow limits. The Standard Ranger with gravity flow and the Fluido with both gravity-driven and pressurised flow achieved the best results within the specified limits, with up to 35 °C. This study also confirms that higher flow rates result in lower output temperatures due to shorter contact times with the heating elements. (41)

This shows that statements made by manufacturers should always be verified by studies like ours, as the promised performance often cannot be achieved, which may lead to potential harm to patients.

Another study tested a **water-bath warmer**, a **dry-heat plate warmer**, and an **intravenous fluid tube warmer** in terms of their heat capacities. In the tests, 0.9% saline solution was administered at 21-23 °C and 3-5 °C at flow rates between 2–100 ml/min. The water bath warmer and the intravenous fluid tube warmer showed an initial rise in temperature at low flow rates, but as soon as the flow was increased, the output temperature of both devices dropped. Furthermore, a difference was noted between the saline solutions administered at 21-23 °C and those with an initial temperature of 3-5 °C at high flow rates in these two devices: At first, a steady increase in temperature was observed. At higher infusion rates a temperature drop of the cooled saline occurred compared to the temperature curve of the fluid at room temperature. Warmer liquids are therefore heated quicker and more efficiently in these devices. Only the dry-heat plate warmer showed no drop in output temperature at higher flow rates and no significant difference between the initial temperatures of the fluids. (42)

In 2003, a study compared the **FMS 2000** (Belmont Instrument Corp., Billerica, MA), the previous model of the Belmont® Rapid Infuser RI-2, and the **Level 1 rapid infusion system** (SIMS Level 1, Inc., Rockland, MA) in terms of their heat capacity, flow rates and air embolism management. Erythrocyte concentrates with an initial temperature of 8 °C were administered at flow rates of 250 mL/min and 500 mL/min. With the lower flow rate, both the FSM 2000 and the Level 1 were able to heat the fluid to ≥ 37 °C. However, at an infusion rate of 500 mL/min, only the FMS 2000 managed to warm the erythrocyte concentrates to physiological body temperature. Also, a progressive decrease of the temperature over time was observed with the Level 1 device. (38)

Another study evaluated **The Hotline** (SIMS Level 1, Inc., Rockland, MA) against **The Ranger** (Arizant Healthcare, Eden Prairie, MN): Saline at a temperature of 21 °C and 10 °C cold erythrocyte concentrates were administered using a pressure system of 90 mmHg and 300 mmHg. Both devices showed comparable flow rates at 90 mmHg and 300 mmHg for each type of fluid. The hotline reached higher output temperatures at lower flow rates (1-4 L/h): under these conditions, saline was administered at 40.5 °C and erythrocyte concentrate at 39.0 °C. (Comparison Ranger: saline: 36.2 °C, erythrocyte concentrates: 34.6 °C). In contrast, the Ranger achieved higher output temperatures at higher flow rates (> 4 L/h): Saline was

administered at 35.0 °C, erythrocyte concentrates at 33.2 °C. (Comparison hotline: saline: 30.1 °C, erythrocyte concentrates: 24.7 °C). This proves that the hotline is not suitable for rapid, pressure-assisted administration of fluids and blood. (43)

In this study, the changes in haemolysis rates before and after warming erythrocyte concentrates using different RIS, could only be examined on an exploratory basis, as the amount of red blood cell concentrates available for testing was limited. (33)

However, a previous study has shown that multiple warming of erythrocyte concentrates has no harmful effects on red blood cells. In this study, erythrocyte concentrates stored at 1-6 °C were warmed five times at 24-hour intervals up to 10, 13 and 22 °C. No significant changes were observed in terms of pH, potassium or free haemoglobin. Furthermore, the haemolysis rate remained below the limit of 0.8%. (35)

However, this does not rule out the possibility that damage to red blood cells may occur under conditions of high flow rates, higher temperatures, and rapid heating of red blood cell concentrates, as seen with RIS. For this reason, the damage to red blood cells caused by the use of RIS should be evaluated more closely in future studies.

In the conducted tests, the AutoMer II showed a slight increase in haemolysis rate, whereas a more significant increase was observed with the Fluido®. In contrast, the Belmont® and the Ranger™ showed a decrease in haemolysis rates. Therefore, no consistent trend can be detected among the devices. The results should be interpreted with caution, as only expired red blood cell concentrates were used, which already exhibit higher haemolysis rates due to storage damage. Furthermore, because of limited availability, it was not possible to carry out statistical analysis. To ensure clinically representative results, further tests should be performed with erythrocyte concentrates while still within their shelf life to confirm the findings. (33)

11 Limitations

The aim of this study was to objectively assess the performance of commonly available RIS. It is important to emphasis, that this study was not intended to criticise the device manufacturers. Instead, it should highlight that clinicians often rely on manufacturer's specifications without evaluating the efficacy of these devices in clinical settings. We intended to provide a useful real-world evaluation of these devices to support clinical decision-making and device selection.

One important limitation of this study is the fact that saline and erythrocyte concentrates differ in their warming capacities: Due to its lower viscosity and more homogeneous composition, saline generally warms faster and more evenly than erythrocyte concentrates, which show higher viscosity and more cellular content. This fact could influence how applicable our results are in clinical situations which involve the administration of blood products.

Furthermore, only the four devices mentioned were examined in this study, although many other devices are currently available.

Another limitation is that, due to limited availability of red blood cell concentrates, only two trials involving erythrocyte concentrates and only five test runs with saline solution were conducted. If more tests had been carried out, this might have affected the final results.

Additionally, the devices were tested under high flow rates to evaluate their warming capacities under extreme operating conditions. Although maintaining near-physiological temperatures at high flow rates is crucial in emergency situations, this may not be representative of everyday clinical settings, where lower flow rates are usually used. Nevertheless, the use of high flow rates was a deliberate decision. This allowed the evaluation of the devices under the most challenging conditions, providing a robust assessment of their performance.

Also, the energy consumption and the waste generation were not investigated in this study.

Despite these limitations, the results provide important insights on how four different RIS perform under high-flow conditions.

12 Conclusion

Significant differences were observed regarding the heat capacity of the RIS tested under high-flow conditions.

When administering cold saline, only the **Belmont® Rapid Infuser RI-2** achieved output temperatures close to physiological levels, with an average of 37.9 °C. The output temperatures of the other devices ranged from 20 to 29 °C.

In the tests which used red blood cell concentrates, all devices generally showed better results in terms of their heat capacity compared to the administration of cold saline. Both the **Belmont®** and the **Fluido® AirGuard, TSC Life** were able to achieve physiological output temperatures. However, the Belmont® was the only one that managed to come close to the target flow rates of 500 mL/min. The remaining devices only achieved flow rates between 180 and 395 mL/min.

This shows that, of the devices tested, the **Belmont®** is the only one capable of rapidly warming fluids to body temperature under high-flow conditions. The Belmont® therefore offers the most efficient heating, though it may also be potentially more harmful regarding haemolysis.

These findings emphasize the importance of selecting an adequate infusion warming device to minimize the risk of hypothermia during the administration of large volumes of cold fluid.

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Notice regarding the use of artificial intelligence:

In this thesis, the following tool was used to optimise the language (grammar and spelling corrections) of the text: ChatGPT (version GPT-5.3), provided by OpenAI, between May 17, 2024, and March 28, 2026; available at https://chat.openai.com.