Hypothermia in trauma

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ABSTRACT

Hypovolaemic shock that results through traumatically inflicted haemorrhage can have disastrous consequences for the victim. Initially the body can compensate for lost circulating volume, but as haemorrhage continues compensatory mechanisms fail and the patient's condition worsens significantly. Hypovolaemia results in the lethal triad, a combination of hypothermia, acidosis and coagulopathy, three factors that are interlinked and serve to worsen each other. The lethal triad is a form of vicious cycle, which unless broken will result in death. This report will focus on the role of hypothermia (a third of the lethal triad) in trauma, examining literature to assess how prehospital temperature control can impact on the trauma patient. Spontaneous hypothermia following trauma has severely deleterious consequences for the trauma victim; however, both active warming of patients and clinically induced hypothermia can produce particularly positive results and improve patient outcome. Possible coagulopathic side effects of clinically induced hypothermia may be corrected with topical haemostatic agents, with the benefits of an extended golden hour given by clinically induced hypothermia far outweighing these risks. Active warming of patients, to prevent spontaneous trauma induced hypothermia, is currently the only viable method currently available to improve patient outcome. This method is easy to implement requiring simple protocols and contributes significantly to interrupting the lethal triad. However, the future of trauma care appears to lie with clinically induced therapeutic hypothermia. This new treatment provides optimism that in the future the number of deaths resulting from catastrophic haemorrhaging may be significantly lessened.

INTRODUCTION

Exsanguination due to catastrophic haemorrhage is the second largest cause of recorded civilian prehospital deaths.[1] Much progress has been made over the last 20 years in understanding the haemostatic system[2] and improving outcomes for patients suffering haemorrhage following major trauma.[3 4] Some of these advances have been in the assessment, management and treatment of the severely injured patient. Damage control protocol, advances in topical haemostatic agents and other methods can provide good survival rates in severely wounded patients[5] or test subjects.[6]

The body achieves haemostasis (the cessation of haemorrhage) through three phases: the vascular, platelet and coagulation phases.[7] This process of haemostasis can be significantly impaired by the lethal triad, which is the name given to three conditions that occur together in patients who have sustained severe trauma leading to hypovolaemia.[8 9] Each condition can significantly worsen the others, compounding the condition and worsening the patient's condition significantly. The three factors/conditions that the triad is composed of are coagulopathy, hypothermia and acidosis.[8 9]

This report will give a brief explanation of the stages of haemostasis, the conditions that the lethal triad is composed of and the effect that these conditions has on the haemostatic process. The report will then explain the physiological responses to hypovolaemia/trauma and explore evidence for the role played by temperature in the treatment of seriously wounded patients. The report will examine the hypothesis that prehospital temperature regulation of patients suffering from traumatically inflicted hypovolaemic shock can break the lethal triad and improve patient outcomes.

HAEMOSTASIS

The process of haemostasis consists of three phases. These phases or processes overlap;[10] indeed, it is difficult to draw a distinct line between the end of one phase and the beginning of another.[7] The first of the haemostatic phases is the vascular phase.[7 11] When a blood vessel is cut or ruptured the smooth muscle fibres in the vessels wall contract. This response is known as vascular spasm.[7] The spasm is caused by the injury to the smooth muscle cells releasing chemicals such as thromboxanes,[10] stimulation of the localised pain receptors and the release of serotonin by anchored platelets.[11] The endothelium that line the blood vessels become sticky, and in small blood vessels the endothelium may stick together occluding the opening.[12] The vascular spasm reduces the size of the blood vessels lumen which slows blood loss, and lasts for a period of about 30 min.[12]

The second phase of the haemostatic process is the platelet phase.[7] In a normal undamaged blood vessel platelets are repelled by the endothelium, but when the endothelium is damaged platelets adhere to exposed collagen fibres and macromolecules in the subendothelial tissues.[11 13] The platelets release chemicals including ADP, serotonin and thromboxane.[10] The release of these chemicals results in increased vascular spasm and the attraction of more platelets to the site.[10] The attracted platelets adhere to those already adhered to the collagen fibres and release their chemicals. This is an example of positive feedback (output being used to enhance the input)[14] and results in a large number of platelets forming a temporary seal.[10] This temporary seal is known as a platelet plug or white thrombus.[11] Adhesion and aggregation of platelets are facilitated by fibrinogen (FI) and a glycoprotein called von Willebrand factor (VWF). VWF is synthesised by endothelial cells and stored in organelles called Weibel-Palade bodies, which are unique to endothelial cells.[13] Upon damage to blood vessels, collagen is exposed. Circulating VWF binds to both the

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exposed collagen and the glycoprotein receptors that are located on the platelet membranes (GP Ib/IX/V receptors).[15] The VWF acts as a form of connecting agent. Both the vascular and platelet phases occur within a few seconds of the injury occurring.[12]

The third phase of the haemostatic process is the coagulation phase.[7] The currently accepted scheme of coagulation is the 'waterfall' or 'cascade' model.[16] In this model, coagulation is reliant on 11 blood plasma proteins and calcium ions: these are known as clotting factors.[12] Coagulation involves a number of steps involving the activation of the clotting factors in a specific order, ultimately resulting in the conversion of circulating FI into the insoluble protein fibrin.[12] The clotting factors react in a form of chain reaction in which the clotting factors (which are proenzymes and procofactors[17]) are converted into enzymes that activate the next clotting factor, until FI is converted into fibrin.[10 13] The resulting fibrin progressively stabilises the platelet plug[10] laying down a fibrin mesh that forms the framework of the blood clot.[11]

The process of the activation of the clotting factors is known as the coagulation cascade.[12 18] The clotting factors are numbered chronologically in order of discovery rather than in the order that they take part in the coagulation cascade.[10] The coagulation cascade can be broken down into three areas: the extrinsic pathway, the intrinsic pathway and the final common pathway.[10 18] Coagulation can be initiated by the intrinsic or extrinsic routes. However, regardless of the initiating route both methods result in the final common pathway[13] (table 1).

The intrinsic pathway is initiated through a series of protease reactions initiated when factors that are present in the blood come into contact with the damaged endothelium (blood vessel lining).[10 13] In this intrinsic pathway no extrinsic clotting factors such as tissue factor (TF) (FIII) are added to the blood.[16] The intrinsic pathway is slower than the extrinsic, taking 3–6 min,[10] and can be evaluated in the laboratory using the activated partial thromboplastin time (PTT).[19] When clotting Factor XII (FXII) comes into contact with an activated platelet (from the platelet phase) it becomes the activated form FXIIa[13] (activated factor enzymes are represented by the suffix 'a').[16] High molecular weight kininogen acts as a cofactor for FXII, helping anchor it to the surface of the activated platelets.[13 20] As FXIIa (a protease) accumulates it converts the inactive prekallikrein in the blood plasma into activated kallikrein.[13] The kallikrein accelerates the conversion of FXII into FXIIa; this process being a form of positive feedback. FXIIa also converts FXI into FXIa which also binds to the activated platelets. FXIa converts FIX into FIXa, which converts FVIII into FVIIIa. The conversion of FVIII by FIXa involves FXa and thrombin, which are downstream products of the cascade.[13] FIXa, FVIIIa and Ca^{2+} ions (from activated platelets) then form a complex called tenase[21] that converts FX into FXa, which is the start of the final common pathway.[13 20]

The extrinsic pathway is initiated through TF (FIII) coming into contact with FVII.[16] TF is a lipoprotein[12] present in all cell membranes with the exception of the vascular system's endothelial cells.[16] If a blood vessel's endothelium is disrupted, allowing contact between the plasma proteins and the tissue cell membranes, TF can activate FVII and form an enzyme complex with the activated factor.[13 16] The FVIIa–TF complex accelerates coagulation significantly (compared with the intrinsic pathway).[16] The FVIIa–TF complex converts FX into FXa, which, as previously stated, is the start point of the final common pathway.[13 20] This pathway can be analysed and evaluated in a clinical/laboratory setting using the prothrombin time (PT).[16 19]

Both the intrinsic and extrinsic pathways result in the activation of FX into FXa. FXa is the start point of the final common pathway, and at this stage the haemostatic process continues along the final common pathway, regardless of whether the activation of FX occurred via the intrinsic or extrinsic route, or as a consequence of both.[13] FXa, along with FV, phospholipids and Ca^{2+} ions, converts prothrombin (FII) into thrombin (FIIa). Thrombin (FIIa) converts FI into soluble fibrin monomers (FIa).[13] These monomers polymerise and trap erythrocytes, platelets and leucocytes.[10] Thrombin (FIIa) activates FXIII converting it into FXIIIa, which stabilises and cross links the fibrin polymers causing the formation of a stabilised fibrin clot.[10 13] Thrombin can also catalyse the activation of prothrombin (FII) into thrombin (FIIa) and can catalyse the formation of FVa and FVIIIa. This amplifies coagulation and is another example of positive feedback.[13] After the clot has formed, the platelets that are stuck in the fibrin mesh contract and release serum. This serum is blood plasma from which the clotting factors are absent. This contraction causes the clot to shrink/retract which pulls the damaged blood vessels walls together, closing off the hole and reducing haemorrhage[10] (figure 1).

Table 1 Clotting factors

Clotting factors	
FI	Fibrinogen
FII	Prothrombin
FIII	Tissue factor (thromboplastin)
FIV	Calcium (Ca^{2+})
FV	Labile factor, proaccelerin, Ac-globulin
FVII	Stable factor, proconvertin
FVIII	Antihaemophilic globulin, antihaemophilic factor A
FIX	Christmas factor, plasma thromboplastin component (PTC), antihaemophilic factor B
FX	Stuart Prower factor
FXI	Plasma thromboplastin antecedent (PTC), antihaemophilic factor C
FXII	Hageman factor
FXIII	Fibrin stabilising factor

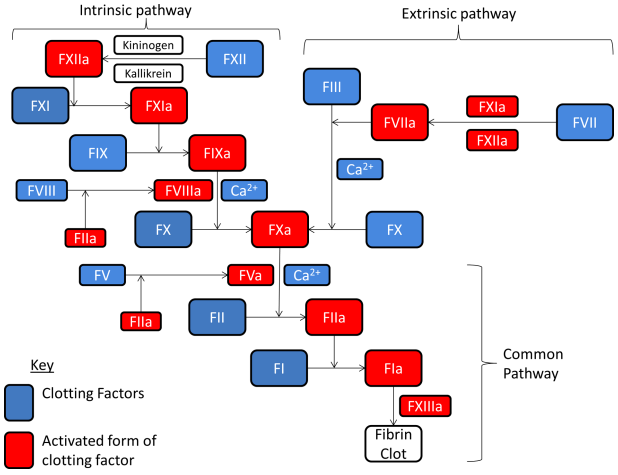

Figure 1 The coagulation cascade. Access the article online to view this figure in colour.

THE LETHAL TRIAD

The lethal triad is a term often used to describe the relationship among hypothermia, acidosis and coagulopathy.[4] Studies have shown that, individually, acidosis and hypothermia can have deleterious effect on coagulation; however, when acidosis is present in conjunction with hypothermia there is a more significant impairment of coagulation than the sum of that caused by the individual conditions.[9 22 23] The presence of hypothermia and acidosis, which results in coagulopathy, and the relationship among these three conditions, can result in a 90% death rate among victims of severe trauma.[24] The lethal triad has also been known as 'the bloody vicious cycle'[25] but the manifestation of coagulopathy, hypothermia and acidosis is unchanged regardless of the term used to describe it. Haemorrhage (internal or external) reduces circulating volume which leads to reduction in core body temperature and hypoperfusion of the tissues. Hypoperfusion causes tissues to become hypoxic and respire anaerobically producing lactic acid. This leads to acidosis of the blood, which in conjunction with hypothermia slows the coagulation cascade causing a loss of clotting ability. Reduced clotting ability is known as coagulopathy.[26] Coagulopathy prevents haemostasis, allowing haemorrhaging to continue. Active haemorrhaging and reduction in the performance of the myocardium (caused by acidosis) cause further heat loss and further hypoxia. Hypothermia and acidosis worsen, which further inhibits coagulation allowing further active haemorrhage.[9 23 25] This continues the progressively worsening cycle, and has severely deleterious effect on the patient's condition.[25]

COAGULOPATHY

Coagulopathy is a term used to describe a group of conditions in which there is a problem with the process of blood clotting.[27] It can be defined quantitatively as PT or PTT time that is >1.5 times normal.[28] Coagulopathy can occur for a number of reasons[27] but this report is focused on coagulopathy that has occurred as a result of trauma. Coagulopathy is a common occurrence in seriously injured patients being present in approximately a quarter of patients suffering from severe trauma.[28] In trauma coagulopathy results due to a combination of blood loss, haemodilution, consumption of platelets and clotting factor and hypothermic and acidotic conditions[29] (these last two conditions are discussed in the next two subsections).

Severe tissue damage, such as that caused by extensive burns, head injury, traumatic amputation or gunshot wounds, can result in disseminated intravascular coagulation (DIC).[30 31] DIC is a form of coagulopathy sometimes known as consumption coagulopathy that can occur in the case of trauma due to inflammation.[31] In cases of DIC clotting factors become abnormally active, resulting in the formation of small clots in blood vessels. These small clots can obstruct blood supply to organs, causing organ damage and possibly organ failure.[31] The use/consumption of the clotting factors by DIC results in a deficiency of these clotting factors when needed to achieve haemostasis allowing further haemorrhage and compounding the condition.[31] The deficiency can cause failure of haemostasis, haemorrhage from minor injuries, haemorrhaging without injury, stroke, organ failure or ischaemia of the limbs.[31] There is debate about whether severe tissue injury causes immediate DIC or acute coagulopathy of trauma shock.[32]

ACIDOSIS

Cellular respiration provides the energy required for cellular function and the maintenance of homeostasis.[12] Under normal circumstances aerobic respiration of oxidative fuels provides this energy in the form of ATP. This is reliant on the supply of oxygen to the respiring tissues being adequate to meet the demand. Hypovolaemia results in decreased oxygen delivery which can lead to cellular oxygen demand exceeding oxygen delivery.[33] Under these hypoxic conditions tissues respire anaerobically. During anaerobic respiration pyruvic acid amasses and is converted into lactic acid.[33] The production of lactate leads to metabolic acidosis.[34] This form of metabolic acidosis is more specifically described as lactic acidosis, a condition in which blood plasma is excessively acidic due to an accumulation of lactic acid.[26]

The clotting factors responsible for coagulation are proenzymes, which become activated enzymes during haemostasis and the coagulation cascade. Enzymes and the reactions that they control are affected by pH. The pH at which the reaction occurs at the fastest rate is known as the optimum pH for that enzyme/reaction.[16] Normally blood is slightly alkaline, with a normal blood pH of between 7.35 and 7.45.[11] Deviation away from normal blood pH ranges can cause the denaturing of clotting enzymes (activated clotting factors), which may have a detrimental effect on coagulation by inhibiting the formation of enzyme substrate complexes.[23] Thrombin generation is impaired by pH levels of below 7.3 and FI degradation is increased by acidosis.[2] Acidosis has been shown by some studies to increase PT and PTT,[35] indicating that acidosis has a slowing effect on both the intrinsic and extrinsic pathways[28] (other studies conducted some years before had results inconsistent with this finding).[36] Reduced clot formation has been shown in normal blood that has been made more acidic (pH7).[37] Acidosis in animal models shows reduced concentration of FI, reduced platelet counts and reduced thrombin (FIIa) generation.[22] The use of recombinant FVIIa also has little effect in cases where patients are acidotic.[38] Acidosis decreases myocardial contractility, reduces cardiac output,[39] causes vasodilation and hypotension, decreases renal and hepatic blood flow and can increase the likelihood of ventricular dysrhythmias.[40] There is some suggestion in the research by Dirkmann *et al*[9] that if acidosis is present without hypothermia it has no significant effect on clot formation. Although this study was conducted on blood samples in vitro, during trauma in vivo blood is likely to be both acidotic and hypothermic.

HYPOTHERMIA

The normal range for human core body temperature is between 35.6°C and 37.8°C.[10] Hypothermia is defined as a core body temperature of less than 35°C.[41] Body temperature is regulated by the hypothalamus, which receives temperature feedback from the peripheral nervous system, and feedback from its own receptors which measure blood temperature.[42] Temperature that falls outside of the normal range causes the activation of heat loss or heat generating mechanisms to bring the body temperature back into the normal range. This is an example of negative feedback.[42] In an individual with a reduced core body temperature (that falls outside the normal range) the hypothalamus stimulates skeletal muscles to shiver, which requires increased cellular respiration to meet the demand for ATP.[11] The increased cellular respiration leads to increased heat production (less than 40% of the energy released through cellular respiration is captured in the form of ATP, most is released as heat).[11] Blood has a major role in the regulation of core body temperature; it absorbs the heat generated in active skeletal muscle and distributes this heat to other tissues (through its circulation around the body). When body temperature is too low, warm blood flow can be restricted

to vital organs such as the brain.[12] This is achieved through the hypothalamus stimulating vasoconstriction of the blood vessels that supply the skin.[11] Blood is also used in the cooling mechanism by carrying heat to the surface of the skin, allowing it to radiate away from the body.[12]

Mild hypothermia causes increased oxygen demands of the tissues (to fuel shivering); however, as the core body temperature reduces further and shivering ceases, the oxygen demands of the tissues are reduced to levels below that required in normothermia.[43] Hypothermia can be provoked in a casualty following trauma in numerous ways, such as: exhaustion, the removal of clothing by medical teams, entrapment, haemorrhage, the administration of cold fluids and the environment.[44] As heat is produced in the body as a product of cellular respiration, this may be decreased by hypoperfusion as a consequence of hypovolaemic shock.[4] Decreased heat production, coupled with the important role played by blood in heat distribution, means that blood loss can have a very rapid, significant negative effect on core body temperature. Cold can also cause a stress response which can increase discomfort, anxiety and pain.[44] A 10-year study of severely injured patients found that on admission early deaths had significantly lower core body temperatures than early survivors.[5]

Hypothermia can cause a left shift of the oxygen disassociation curve (causing haemoglobin to release oxygen less readily), reduced cardiac output and cardiac arrhythmias.[34] Hypothermia also impairs coagulation;[9] both PT and PTT increased in samples taken from hypothermic patients, animal models[22] or blood samples that have been cooled outside of the body (in vitro).[9] Temperature, like pH, has a significant effect on the rate of enzyme controlled reactions.[45] Higher temperatures provide more kinetic energy which causes more random collisions between enzymes and substrates. This allows the formation of more enzyme–substrate complexes which results in an increased rate of the formation of products. The temperature increase will only increase the rate of reaction up until it causes the enzymes to denature. The temperature at which an enzyme controlled reaction happens fastest is known as the optimum temperature.[45] The activated clotting factors (enzymes) optimum temperature is 37°C (normal body temperature).[4] Hypothermia prolongs these coagulation cascade enzyme reactions leading to increased coagulation times.[28] Reduced temperature also has an effect on non-enzymes that play very important roles in haemostasis (such as platelet adhesion and aggregation) such as the glycoprotein, VWF, and its interactions which lead to the formation of the GPIb/IX/V/VWF complex.[46] Hypothermia has been shown to have severe consequences for the trauma patient; in a study of 71 trauma patients a core body temperature of below 32°C on admission was associated with a zero patient survival rate.[47]

PHYSIOLOGICAL RESPONSE TO TRAUMA

Initially when suffering from hypovolaemic shock the body will compensate in order to maintain homeostasis.[48] The body acts through the sympathetic nervous system[10 12] to maintain blood pressure and conserve fluid in order to allow adequate tissue perfusion. This is achieved in the short term by increasing heart rate, constricting blood vessels and reducing fluid lost through other bodily functions.[10 12 45 48]

The heart rate is controlled by the cardiovascular centre (CVC) located in the medulla and pons areas of the brain.[12] Peripheral and central receptors detect changes in systemic blood pressure or blood chemistry.[48] Baroreceptors located in the carotid sinuses and the aortic sinuses are sensitive to pressure changes within blood vessels.[10] A drop in blood pressure (caused in this case by blood loss) reduces baroreceptor discharge.[12] Reduced baroreceptor input activity to the CVC increases sympathetic nervous system drive to the heart, leading to an increase in heart rate and increased strength of cardiac contraction.[45] Baroreceptor inhibition also stimulates the vasomotor centre located in the medulla oblongata which results in vasoconstriction.[12]

Chemoreceptors located in the carotid and aortic bodies are sensitive to blood pH (and therefore blood carbon dioxide and oxygen levels).[45] Chemoreceptors on the medulla oblongata detect chemical changes in the cerebrospinal fluid.[12] Increased blood carbon dioxide, reduced blood oxygen levels or reduced blood pH (increased acidity) are signs of inadequate tissue perfusion (caused in this case by blood loss) that are detected by the chemoreceptors.[10] Initially this stimulates the respiratory centre, which increases the respiratory rate. However, in cases of severe respiratory disturbance, or when systolic arterial blood pressure drops below 80 mm Hg,[10] chemoreceptor input to the CVC results in output. The chemoreceptor prompted CVC output is the same sympathetic response as that prompted by the reduced baroreceptor input, resulting in increased heart rate and stronger cardiac contractions.[12] Chemoreceptors like baroreceptors can also stimulate the vasomotor centre resulting in vasoconstriction.[12] The vasomotor centre uses vasoconstriction as a means to mobilise the venous reserve. This is a quantity of slow moving venous blood in the liver, skin and bone marrow. The venous reserve can maintain normal blood pressure and peripheral flow after blood loss of up to 20% of circulating volume.[12]

Respiratory rate and heart rate are closely coordinated systems. This is important because increasing heart rate will not be beneficial if blood is not adequately oxygenated.[12] Increased respiratory rate does, however, also have the beneficial action of accelerating venous return, which is due to the actions of the respiratory pump.[12] The heart rate and vasoconstriction are also further increased by the release of adrenaline and norepinephrine from the adrenal medulla.[48] The release of these catecholamines is triggered by the hypothalamus region of the brain, and potentiates and sustains the actions of the sympathetic nervous system.[10 48] Vasoconstriction causes a reduction in secretion of fluids by the alimentary canal (and its associated glands) and also reduces the amount of fluid lost through the skin as sweat.[48] The conservation of fluid is further aided by the release of antidiuretic hormone from the posterior pituitary gland in response to the stimulation of osmoreceptors (by a change in blood osmotic pressure caused by blood loss) in the hypothalamus. The release of antidiuretic hormone increases the amount of water reabsorbed by the kidneys, increasing the amount of water in the blood and increasing blood pressure (figure 2).[10 12 45]

These actions compensate for circulating fluid loss in the lower stages of hypovolaemic shock, but if a large volume of circulating fluid is lost the compensatory mechanisms are exceeded and the patient moves into the higher (more severe) stages of hypovolaemic shock (table 2).[48] Failure of the compensatory mechanisms leads to gross hypoperfusion of tissues, ultimately leading to cardiac arrest and/or hypoxic ischaemia.[48] In conditions of normothermia, critical cerebral ischaemia time (after which infarction will occur) is less than 5 min[49] and critical cardiac ischaemia time is near to 20 min[50]

COMPLICATIONS OF FLUID RESUSCITATION

Prehospital fluid replacement is generally carried out using crystalloid fluids.[51] Crystalloid fluids are easy to store, inexpensive

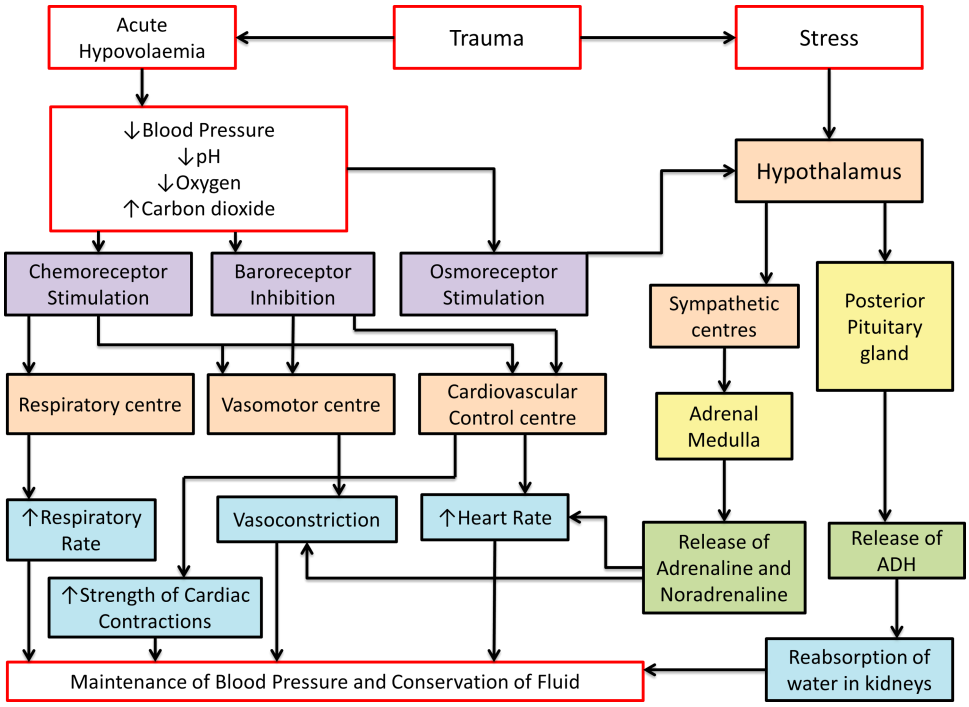

Figure 2 Compensatory mechanism. ADH, antidiuretic hormone. Access the article online to view this figure in colour.

and can be easily warmed.[52] When used correctly crystalloid fluids have a good safety record,[52] but the practice of intravenous crystalloid fluid administration can cause significant worsening of the three factors that form the lethal triad.[53] The use of cold fluids can worsen hypothermia[23] and can also increase haemodilution which worsens coagulopathy.[2] Overly aggressive fluid administration can increase blood pressure and dislodge clots that are forming or have already formed;[23] this is often informally referred to as 'blowing out clots'. During the Vietnam war, the American military used aggressive fluid resuscitation, which did sustain some vital organ function but caused deaths due to acute respiratory distress syndrome.[51] More recently the concept of permissive hypotension,[52] in which fluid administration is limited to maintain a radial pulse (approximately 90 mm Hg systolic blood pressure), has become well practised in both military[53–55] and civilian[56] prehospital and hospital settings.

Reperfusion injury can also be a significant complication in fluid replacement.[33] Reperfusion injury occurs when perfusion is re-established to an area that has been ischaemic. In tissues deprived of oxygen transport, mechanisms across cellular membranes and the membranes of organelles, such as the mitochondria, are disrupted.[57] Ca^{2+} transportation out of both the mitochondria and the cell itself is compromised because the hypoxic cell does not have adequate oxygen to produce the ATP required to pump Ca^{2+} out of itself and its organelles. When circulation is restored these conditions result in oxidative damage, which prompts the inflammatory response and involves the mechanisms of apoptotic cell death.[57] These factors can result in acute respiratory distress syndrome[33 58] (as previously mentioned with regard to the Vietnam war) and multiple organ failure syndrome.[58]

Table 2 Stages of hypovolaemic shock

	Stage 1	Stage 2	Stage 3	Stage 4
Blood loss (%)	<15	15–30	30–40	>40
Blood loss (cm^3)	<750	750–1500	1500–2000	>2000
Pulse rate	<100	>100	>120	>140
Respiratory rate	14–20	20–30	30–40	>35
Blood pressure	Normal	Decreased	Decreased	Decreased
Mental state	Normal/slightly anxious	Mild anxiety	Confusion and Lethargy	Confusion

BENEFITS OF WARMING

The link between hypothermia on admission to medical facilities and low survival rates is significant.[5 47] Most guidelines for the treatment of coagulopathy in acute haemorrhage, including Advanced Trauma Life Support protocols, recommend warming of patients.[23 28 53 59 60] Prehospital measures such as rapid control of external haemorrhage, removal and replacement of wet clothing, insulating blankets (foil and conventional materials) and active warming can all be used to prevent/delay the onset of hypothermia in the trauma patient.[53] Active warming of the hypothermic patient can be achieved through equipment that heats intravenous fluids,[28] and through external heat packs[44] or mechanical heater systems.[28] For instance, a Swedish study of trauma patients found that patients who were actively warmed with external heat packs during transport had statistically significant reductions in both heart and respiratory rates.[44] The American military has recognised the importance of addressing hypothermia in trauma and has reduced the proportion of hypothermic admissions to its higher role combat support facilities from 7% to less than 1%.[61] This was achieved through the hypothermia prevention measures/equipment and protocol listed above.[53]

The maintenance of normothermia provides the optimum conditions for haemostasis[4] and has been shown to improve survival in animal models. A study in which 40 rats were subject to 40% volume blood withdrawal over a 60 min period showed better survival rates among the group subject to active warming, when compared with the non-warmed control group. The conclusion of this study was that 'warming during haemorrhage prevented exacerbation of hypothermia and therefore improved survival.'[62] Thus, there is significant evidence that active warming of trauma patients can improve outcomes when compared with control groups,[44 62] as maintaining normothermia can help to prevent the risks associated with hypothermia induced coagulopathy.[59]

CLINICALLY INDUCED HYPOTHERMIA

It has been suggested that there are significant differences between spontaneous hypothermia and therapeutic (clinically induced) hypothermia.[33] Spontaneous hypothermia in this context is the type that would be found in a patient following blood loss in trauma (as described earlier). Clinically induced hypothermia, however, is hypothermia induced in a controlled manner to prevent ischaemic insult to tissues.[33]

Clinically induced hypothermia has been shown to have a positive effect in preserving neurological function in traumatic brain injury[63] and is being investigated for possible benefits in cases of cardiac arrest.[33] An important issue when using clinical hypothermia in cases of hypovolaemia following trauma is the negative effect it might have both on coagulation and as a contributing factor in the lethal triad (issues that would be less important in non-trauma patients without major haemorrhage). Clinically induced mild hypothermia does seem to differ significantly from spontaneous hypothermia;[33] indeed, studies of both small[64] and large[65] animal models have shown positive results in cases of therapeutic hypothermia in hypovolaemic test subjects. A Japanese study conducted on 24 rats concluded that mild therapeutic hypothermia did not cause coagulopathy during haemorrhagic shock, but did impair coagulation during fluid resuscitation. This impairment was most likely due to haemodilution.[64] It was found that hypothermia prolonged survival after the haemorrhagic shock, that is, 72 h following the blood withdrawal only five of the 12 normothermic test group had survived compared with 10 of the 12 rats that made up the therapeutic hypothermia test group.[64] This study used blood withdrawal, which may not accurately reflect uncontrolled haemorrhage following major trauma, but it does indicate that therapeutic hypothermia may be beneficial in hypovolaemic patients. Studies have also been carried out on swine models. In one such study hypothermia was found to significantly decrease death rates.[65] However, this study was also limited by using blood withdrawal. Studies using blood withdrawal might not accurately replicate real time trauma, in which the cessation of haemorrhaging is reliant on the process of haemostasis.

Induced hypothermia can prevent ischaemic damage to tissues.[33] The protective attributes of therapeutic hypothermia result from the reduction in metabolic activity that it causes, preserving cellular energy in the form of ATP. Hypothermia can reduce demand for ATP significantly.[33] A large amount of ATP is required by Na^+/K^+ ATPase pumps to move both sodium ions out of cells and potassium ions into cells against concentration gradients (a function essential for transmission of impulses by nervous cells).[10 12 45] Clinically induced hypothermia reduces the activity of these pumps considerably, thus reducing ATP requirements.[33] Therapeutic hypothermia reduces both the inflammatory response and tissue death (as already described under reperfusion injury); however, a possible side effect of hypothermic inflammatory suppression is that it can increase the risks of infection.[66]

The use of chitosan based topical haemostatic agents has been shown to effectively control haemorrhaging in hypothermic conditions.[6] An interesting result in the two control groups of the study into hypothermia and the effectiveness of chitosan based haemostatic agent showed a survival rate of 75% among haemorrhaging hypothermic models when compression was used (without haemostatic agent) to arrest bleeding. In comparison, normothermic haemorrhaging models showed a 50% survival rate when compression was used (without haemostatic agent) to arrest bleeding.[6] In both the hypothermic and normothermic groups using the haemostatic agent to arrest bleeding, a 100% survival rate was achieved.[6] The difference in the survival rates using compression alone may indicate the potential benefits of induced hypothermia in a test that allows free bleeding instead of blood withdrawal. Hypothermia can reduce the effects of inflammation and lengthen the time taken for serious ischaemic insult to occur and may well be used in the future to extend the time available for damage control surgery to take place.[33]

CONCLUSIONS

Hypothermia is a key factor in the lethal triad, adding to problems with coagulation and exacerbating the vicious cycle that is the triad.[4 25] Evidence suggests a significant difference between spontaneous onset hypothermia following trauma and clinically induced therapeutic hypothermia.[33] Therefore, in the interests of clarity, it seems apparent that when discussing the lethal triad, the term hypothermia should be redefined as spontaneous hypothermia. Current guidelines[23 28 53 59 60] recommend the warming of trauma victims, to try and maintain a state of normothermia and prevent the onset of post trauma spontaneous hypothermia. The maintenance of normothermia allows coagulation to occur at the optimum temperature for the enzymes (clotting factors) involved.[4] This coagulation is an essential part of achieving haemostasis, which in turn prevents the worsening of heat loss through bleeding, and prevents the worsening of hypoxia (and the worsening of the acidotic consequences of the hypoxia). In doing so maintaining normothermia can interrupt the lethal triad, improving survival rates. Hess states that 'preventing the coagulopathy of trauma is best accomplished by preventing injury and hypothermia'.[29]

Hypothermia prevention can be achieved through a number of means including the active warming of patients.[44 53 62] Equipment is available for use in the prehospital setting, with the US military demonstrating that prehospital measures can cause a large reduction in hypothermic admissions, even given the additional complexities that arise in areas of conflict.[61] In short, active warming of prehospital hypovolaemic trauma victims can improve outcomes.

There is also significant evidence that suggests clinically induced therapeutic hypothermia may be of benefit in improving outcomes in cases of hypovolaemic trauma.[64] Current doctrine describes the 'golden hour' in which critical medical interventions can save a patient's life.[67 68] It appears likely that in the future this golden hour may be extended through induced hypothermia, allowing a greater window of opportunity to perform lifesaving interventions such as damage control surgery.[33] The extension of the golden hour through clinically induced hypothermia has already been labelled 'emergency preservation and resuscitation'.[33]

Although hypothermia can reduce coagulation, the extra time it could provide for effective treatment may well outweigh its negative effects. The reduction it causes in haemostasis can be offset by the use of topical haemostatic agents and modern military type tourniquets, which work well despite low patient core body temperature.[6] The use of these methods coupled with future advances in emergency preservation and resuscitation look set to revolutionise treatment of hypovolaemic trauma victims. Therapeutic hypothermia can increase critical ischaemia times and improve survival rates in cases of trauma and polytrauma,[33] which will undoubtedly lead to its becoming an integral part of trauma care.

More research is required to examine and refine how hypothermia can be utilised in a prehospital and emergency department setting. There is undoubtedly a need for quite complex protocols for clinically induced therapeutic hypothermia[33] and a need for greater understanding at a cellular and subcellular level of trauma and the conditions/factors it involves.[34] Despite the need for greater understanding, there is already equipment in existence that could facilitate prehospital cooling,[33] with Beekley suggesting that in the future that the 'ultimate damage control approach' could be 'suspended animation'.[53] This view is shared by the author who suggests that hypothermic treatment will become an important method of treating trauma, both in the prehospital and hospital stages.

As discussed throughout this report, both clinically induced hypothermia and warming to maintain normothermia are beneficial to trauma patients. Research supports the hypothesis that prehospital temperature regulation of patients suffering from traumatically inflicted hypovolaemic can break the lethal triad and improve patient outcomes. Clinically induced hypothermia is not yet at the stages where it can be effectively used prehospital although it looks set to become a major component in trauma care over the coming years. Spontaneous hypothermia following haemorrhage is deleterious to the patient; it is a major factor in the lethal triad and is associated with poor outcome. Prehospital, aggressive attempts should be made to maintain normothermia, with prompt intervention to arrest haemorrhage, measures to limit exposure to the environment and active warming important practises in breaking the lethal triad and improving patient outcomes.

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Hypothermia in trauma

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Notes