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A whiter shade of pale: the ongoing challenge of haemorrhagic shock

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And so it was that later
As the miller told his tale
That her face at first just ghostly
Turned a whiter shade of pale

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HISTORICAL PERSPECTIVES

THE DARK AGES

Fifty years ago, Procol Harum released their timeless popular music classic based on a number of Johann Sebastian Bach's compositions. Although the lyrics have been matter of debate, the last two lines of the chorus describe succinctly the transient or non-responder to massive haemorrhage. Of all fatalities from trauma, haemorrhage remains the most common potentially reversible cause of early death, especially after penetrating trauma [1], and has plagued surgeons for centuries. The first documentation of trauma deaths occurred in Homer's Iliad written in 700 BC wherein a mortality rate of 79% was documented in 147 patients (Table 1).

Although causing potential haemorrhage, the majority of deaths from arrow wounds most likely arose from hollow visceral abdominal perforation and sepsis. Sling shots were associated with devastating central nervous system damage, the David and Goliath syndrome. Slingers were exceptionally skilful, could hit a bird in mid-flight and cause critical injury at a distance of two hundred metres. The missiles could penetrate to a substantial depth, special instruments being devised by the Romans for their removal. By the very nature of their design, spear thrusts and sword strikes would result in major vascular injury, the latter causing instant amputation and fatal haemorrhage.

Table 1. First documentation of trauma deaths occurred in Homer's Iliad

Injury mechanism	Number of patients	Mortality (%)
Sword strike	17	100
Spear thrust	106	80
Sling shot	12	66
Arrow	12	50
Total	147	79

THE RENAISSANCE

For a long period in time little or nothing changed. John Collins Warren, the surgeon who operated in the first public demonstration of ether anaesthesia by Morton in 1847, described shock as, "A momentary pause in the act of death". His compatriot Samuel Gross considered the physiological consequences as, "The rude unhinging of the machinery of life", a definition of multiple organ dysfunction that has yet to be surpassed. Although Gross realised that external haemorrhage must be controlled by tourniquet, he conceded that, "Internal haemorrhage is more dangerous than external, because it is generally inaccessible" [2].

Due to the effect of hypoperfusion on the central nervous system the pathophysiology was considered initially to

be nervous in origin, resulting in descriptions such as, "great nervous depression" or "a sudden sinking of vitality" [3]. Even following the invention of the blood pressure cuff by Riva-Rocci in 1896, hypotension was not equated with blood loss but was considered to result from a "general perturbation of the nerves". This was assumed to result in vasomotor dysfunction and arteriolar vasodilatation with the pooling of blood in the splanchnic bed accounting for the reduced blood pressure. In an effort to counteract neural dysfunction stimulants such as caffeine, alcohol, ammonia, and turpentine were prescribed. Paradoxically, bleeding by venesection was also advised.

MODERN TIMES

Although the vasomotor dysfunction and blood pooling theories persisted during the First World War, intravenous fluid resuscitation became recognised as an essential intervention. While saline was considered the fluid of choice, the effect was often transient and synthetic colloids in the form of gum acacia in a weak 0.19% saline carriage solution were employed. Unfortunately, this was associated with major febrile reactions and other morbidities and fell out of favour. Although blood was considered essential, the maximum volume necessary was considered to be only 600 mL. Blood typing was performed prior to transfusion but despite the discovery of the A, B and O blood groups by Landsteiner in 1901, and the AB group one year later by Decastello and Sturli, haemolytic reactions were still a common complication, thus limiting blood usage. The Rhesus factor was only described by Landsteiner in 1937. Only after the Great War were the neural and splanchnic theories dispelled by the work of Blalock who proposed that shock was a result of hypovolaemia and a mismatch of intravascular volume and capacitance [4]. This and further developments in blood transfusion heralded a new era in the resuscitation of major haemorrhage.

THE NEW AGE

The seminal although perhaps methodologically flawed work of Shires *et al.* [5] brought forth the concept of third space loss, a fluid black hole which required large volumes of crystalloid in addition to blood transfusion for successful resuscitation. Crystalloid was proposed in volumes of three times the predicted blood loss to achieve an adequate intravascular volume [5]. Thus was born the crystalloid-colloid controversy. Hamilton Bailey [6] condemned the use of crystalloids stating, "The use of salt water for resuscitation causes the tissues to rebel until the patient is literally drowning. Plasma, on the other hand, achieves the rapid restoration of adequate blood flow. It is the resuscitation fluid of choice". Both crystalloid and colloid protagonists however, overlooked one simple fact. Neither of these fluids transports oxygen and the underlying pathophysiology of haemorrhagic shock is a profound reduction in oxygen delivery which results in anaerobic metabolism, a lethal acid base disorder for aerobic organisms [7, 8].

TOWARDS A BETTER UNDERSTANDING

ENERGY PRODUCTION

In human beings, ninety percent of inhaled oxygen goes toward the formation of adenosine triphosphate (ATP) by oxidative phosphorylation, and this is virtually the sole energy source for the myriad of energy-requiring reactions. ATP is not stored, there being on average only 100 grams immediately available. During normal aerobic metabolism via Krebs cycle and the electron transport system within the mitochondria, ten million molecules of ATP are turned over per cell every second. The total daily mass of ATP production may amount to a staggering 100 kg. The molecular weight of ATP is 0.5 kg which contains Avogadro's number of molecules, namely 6×10^{23}. This is the number of cupsful of water in the Pacific Ocean [9]. The daily mass of 100 kg is therefore two hundred times this number and amounts to 12×10^{25}, the number of cupsful of water in two hundred Pacific Oceans. During profound haemorrhage, ATP production may be reduced by as much as 95%. In a most elegant experimental model using liver sections coated with pulverised firefly light organs which are illuminated by ATP, Paxian *et al.* [10] demonstrated a progressive and profound reduction in ATP concentrations with varying degrees of haemorrhage. Prolonged hypotension resulted in apoptosis and necrosis, Toll-like receptor down-regulation, the formation of reactive oxygen species (ROS), and endothelial dysfunction. Limited amounts of ROS are produced during normal mitochondrial metabolism but are removed by endogenous antioxidants. When produced in excess these highly reactive molecules cause mitochondrial and host cell injury. In those with massive haemorrhage, this emphasises the need for rapid reversal of anaerobic metabolism.

RESUSCITATION PROTOCOLS

More than 2,000 years ago the Hindu doctrines of Sushruta Samhita (circa 700 BC) stated, "The best treatment of any lost substance is replacement by an identical expander". It has taken more than two millennia for us to realise that patients sustaining major haemorrhage do not lose saline, Ringer's lactate or synthetic colloids but rather whole blood. As such, protocols for resuscitation after massive blood loss now advocate minimising the use of clear fluids and employing ratios of packed red blood cells, plasma and platelets in those approaching, although not identical to, the constituents of whole blood [11, 12]. Experience in military conflicts suggests that the optimal ratio in units of

packed red blood cells, plasma, and platelets is 1:1:1 with the addition of cryoprecipitate as indicated, and these data have been extrapolated to the civilian trauma arena with a consistent improvement in survival [13, 14]. In addition to the replacement of coagulation factors, plasma aids in the restoration of the endothelial glycocalyx, thus minimising transcapillary fluid loss into the interstitial space [15, 16]. With no knowledge of the glycocalyx, Hamilton Bailey's statement that plasma should be the resuscitation fluid of choice showed remarkable insight. The optimal ratio has yet to be determined. In the PROPPR study, Holcomb *et al.* [14] randomised patients to a 1:1:1 ratio of PRBC to plasma to platelets versus a 2:1:1 ratio. The only significant finding was a 5.4% reduction in acute exsanguination favouring the 1:1:1 ratio but no difference in 24-hour or 30-day mortality. Despite this, the authors recommend using the 1:1:1 ratio, a conclusion that is unfounded based on their results and which will lead to overuse and wastage of an expensive, and in resource-constrained settings, limited commodity.

COAGULOPATHY

Overzealous use of blood and component therapy is not without danger [17] while the precise requirements should be quantified objectively. Haemostasis involves an interaction amongst the endothelium, platelets, fibrin, clotting factors, and red blood cells. The standard laboratory coagulation tests performed on platelet and cell free plasma at 37°C, do not reflect the in-vivo haemostatic process and, if abnormal, cannot determine the underlying defect. Furthermore, the International Normalised Ratio, prothrombin time and partial thromboplastin time assess only the initial phase of coagulation and not the progression of clot formation or fibrinolysis [18]. Thromboelastometry assesses coagulation in whole blood and has gained acceptance as the optimal point of care tool by graphically illustrating each phase of coagulation [19–22]. This allows a directed choice of the necessary interventions. This is especially true with the recent description of the Acute Coagulopathy of Trauma Shock (ACoTS) [23]. Although the original intent should be to achieve the recommended ratio, in addition to thromboelastometry the clinical scenario must also be taken into consideration. Those in whom total source control of haemorrhage can be achieved surgically, such as splenectomy for splenic trauma, may not require the full protocol, whereas liver or pelvic injury which necessitates packing with the risk of ongoing haemorrhage will undoubtedly need all components in the optimal ratio. Furthermore, the presence of a severe acidosis and hypothermia compromise coagulation and these physiological derangements will also dictate the necessity for specific therapeutic interventions. Based on the volume of blood required or lost, a number of definitions of massive blood transfusion have been proposed but none stipulate the desired end points of resuscitation. With regard to coagulation, laboratory values of a platelet count of > 50,000, fibrinogen > 1 g L^{-1}, and an ionised calcium level of > 1 mmol L^{-1} are recommended, although thromboelastometry is invaluable in determining whether these are sufficient. Based on rheology, the optimal haemoglobin for oxygen delivery is 10 g dL^{-1}. The European guidelines suggest between 7–9 g dL^{-1} based on the TRICC study [24]. Inclusion criteria in this trial, however, were patients with stable organ dysfunction and normovolaemia, while the exclusion criteria were those with ongoing blood loss or transfusion of more than three units of packed red blood cells within the previous 12 hours. As with studies on intravenous fluid management in the critically ill, data from such a study cannot be extrapolated to the acute resuscitation phase [22].

PERMISSIVE HYPOTENSION

Traditionally, the resuscitation and surgical premises were to restore blood pressure and perfusion before surgery and, intraoperatively, to reconstruct the anatomy to completeness. In the presence of a transient response to resuscitation or ongoing physiological derangement, such an approach was associated with a prohibitive mortality rate. A paradigm shift has occurred whereby in the presence of persistent haemorrhage, permissive hypotension is accepted until surgical control can be achieved [21, 25]. There is a fine line however, between the timing of surgical intervention and an irreversible physiological abyss from which there is no return. The optimal systolic or mean arterial pressures for permissive hypotension are unknown [21]. Systolic pressures greater than 80–90 mm Hg are associated with rebleeding and there are no data on the minimum mean pressure required to preserve perfusion of vital organs. Whatever pressure is chosen, the shortest time to operative intervention is an absolute necessity. Operative damage control consists of stopping haemorrhage and controlling contamination while the operative time should not exceed 90 minutes. Thereafter, the patient should be transferred to an intensive care unit for further resuscitation before being returned to theatre for definitive surgery. Although hailed as innovative in the past two decades, Gross made the same suggestion in 1861 when he stated, "The indications presented in all wounds, of whatever nature, are first to relieve shock, secondly to arrest haemorrhage, thirdly to remove foreign matter, fourthly to approximate and retain the parts, and fifthly to limit the resulting inflammation" [2].

ANTIFIBRINOLYTICS

Following the CRASH-2 trial [26] tranexamic acid has been adopted by many trauma centres and even advocated in the pre-hospital environment, although without proof of benefit. Despite demonstrating a reduction in early deaths, a

propensity score-matched study from Europe on the use of tranexamic acid in the pre-hospital environment could show no difference in the 30-day or in-hospital mortality rate, nor in transfusion requirements [27]. This is at complete odds with the further analysis by the CRASH-2 authors who state that tranexamic acid should be given as early as possible to bleeding trauma patients [28]. In the most critically injured cohort this drug may actually increase mortality [29]. Although tranexamic acid is an antifibrinolytic procoagulant, less than 5% of trauma patients suffer from fibrinolysis. The enthusiastic acceptance of the CRASH-2 results is perhaps rather premature. The reduction in all-cause mortality was only 1.5%, while the risk of death from haemorrhage was 0.8%. Although both were mathematically significant, to some this would be considered clinically irrelevant [30]. Caution has been advocated by some until the gaps in knowledge have been filled [31].

BIOMARKERS

The return to aerobic metabolism and normal oxygen consumption is the end point of acute resuscitation. That said, although the oxygen deficit may have been restored by normalising oxygen delivery and consumption, there may still exist an oxygen debt [7]. This is best estimated by serial lactate or base deficit measurement. Rapid return to normal pre-shock values is associated with improved survival rates whereas a delay of more than 36 hours increases the mortality rate substantially [32]. The reasons for persistent elevations in lactate lie within the microcirculation where persistent shunting results in some tissues remaining underperfused with a reduction in oxygen extraction [33]. In addition, nitric oxide which is produced in excess during shock [10, 33] has a higher affinity than oxygen for cytochrome-c, an essential component in the movement of electrons between complexes III and IV of the electron transport system. Base deficit may also serve as a useful indicator of the risk of a coagulation disorder, the success of resuscitation, and as a prognostic marker [12, 34]. Lactate may also indicate the optimal time for definitive fracture fixation. Surgery in those with a persistent elevation despite normal haemodynamics fare much worse than those in whom the serum lactate has normalised [35]. A sustained rise indicates occult hypoxia and persistent ischaemic tissue beds.

FLUID OVERLOAD

In the critically ill or injured, a positive fluid balance is associated with an increased mortality rate and the emphasis has shifted to a more conservative policy [36]. Four phases of fluid management have been proposed using the acronym "ROSE", describing Resuscitation, Optimisation, Stabilisation and Evacuation [22, 37]. In the acute resuscitation phase, regardless of which fluids are used, a positive balance is inevitable due to a number of factors: the necessity to replace lost intravascular volume; the normal metabolic response to injury; and loss of the endothelial glycocalyx which results in fluid leakage into the interstitial space. Following successful resuscitation, patients enter a period of variable haemodynamic instability and organ dysfunction. At this point, judicious fluid management is critical. Liberal use of clear intravenous fluids when not necessary to maintain intravascular volume and tissue perfusion result in generalised oedema and the polycompartment syndrome. In the stabilisation phase, fluids should be required only for maintenance or the replacement of abnormal losses. A spontaneous diuresis heralds the evacuation phase and results from restoration of the endothelial glycocalyx and a shift of fluid from the interstitial to the intravascular compartment. In some patients, despite improving organ function, a positive fluid balance persists and diuresis fails to materialise. The temptation is to achieve this by pharmacological means using albumin, loop diuretics or renal replacement therapy and caution should be exercised. The failure to diurese spontaneously most probably reflects persistent derangement of the endothelial glycoclayx and a forced diuresis may result in hypovolaemia and further organ damage. At present, there is no reliable evidence to support forced de-resuscitation [37].

THE NEXT STEPS

What of the future? If anaerobic metabolism and mitochondrial dysfunction results in ATP depletion and a fatal insult, then it would be logical to follow avenues to reverse this. In this regard, there are two possibilities, namely induce mitochondria to function anaerobically or provide ATP directly [8]. Despite an adequate oxygen delivery, mitochondrial dysfunction may persist whereby oxygen utilisation for energy production is inefficient, the phenomenon of cytotoxic hypoxia [33, 38, 39]. This may arise from pathological shunting in the microcirculation, or possibly the concept of mitochondrial hibernation, an adaptive function during stress where essential functions are down-regulated with a reduction in oxygen and ATP consumption [39]. There are five potential target sites to improve mitochondrial function, namely substrate and co-factor provision, antioxidants and ROS scavengers, as well as mitochondrial membrane stabilisers [38]. Each of these interventions act at different sites in the five complexes of the electron transport system located on the inner mitochondrial membrane. Experimental studies in sepsis have demonstrated a reduction in organ dysfunction and increased survival with targeted strategies at each point in the electron transport chain. The critically injured patient who requires vasopressor support is little different from those with septic shock, with the exception that antimicrobials are of no use [40]. Current theories suggest that severe injury exposes mitochondria, which are intracel-

lular structures, to the immune system. Mitochondria are considered to have evolved from bacteria, most probably the α-Proteobacteria [8] and the immune system reacts as it would to any bacteria by the innate damage associated molecular pattern (DAMP) response [41–43]. Mitochondrial DNA concentrations several thousand times greater than normal have been recorded in the plasma of critically injured patients [44]. As such, the data from sepsis experiments may be applicable to the critically injured.

ATP is the sole source for 95% of energy requiring cellular mechanisms. Due to the profound depletion of ATP following major haemorrhage as a result of mitochondrial dysfunction, the exogenous provision of ATP would seem to be the most logical solution. By itself, intravenous ATP has deleterious effects due to chelation with magnesium and calcium which results in detrimental haemodynamic consequences. Furthermore, rapid deamination and dephosphorylation occurs, with minimal amounts reaching the tissues [8, 38]. When combined with magnesium chloride, however, this compound is protected from degradation while experimental studies have demonstrated a reduction in organ ischaemia, and improved myocardial and endothelial function [8]. Even with successful conventional resuscitation, ATP concentrations may remain depressed for 48 hours while the administration of ATP-$MgCl_2$ after resuscitation may also be beneficial [45]. Nanotechnology for drug delivery has gained much interest and success [46, 47] and if nanotechniques could be developed to ensure ATP delivery to cells in shock, the consequences could be revolutionary. Mechanical ventilation would be unnecessary for oxygenation and simply be required to prevent lung atelectasis and enable CO_2 removal, although this could be achieved by extracorporeal methods. Blood transfusion would be relegated to the history books although component therapy may still be required to address coagulopathy. All that would be required would be a cardiac output to deliver ATP. If this could become reality, for those suffering haemorrhagic shock who reach hospital, the difference in outcome would be dramatic.

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