“Blood failure” time to view blood as an organ: how oxygen debt contributes to blood failure and its implications for remote damage control resuscitation

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Hemorrhagic shock is both a local and systemic disorder. In the context of systemic effects, blood loss may lead to levels of reduced oxygen delivery (DO2) sufficient to cause tissue ischemia. Similar to other physiologic debts such as sleep, it is not possible to incur a significant oxygen debt and suffer no consequences for lack of timely repayment. While the linkage between oxygen debt and traditional organ failure (renal, hepatic, lung, and circulation) has been long recognized, we should consider failure in two additional linked and very dynamic organ systems, the endothelium and blood. These systems are very sensitive to oxygen debt and at risk for failing, having further implications on all other organ systems. The degree of damage to the endothelium is largely modulated by the degree of oxygen debt. Thus hypoperfusion is believed to begin a cascade of events leading to acute traumatic coagulopathy (ATC). This combination of oxygen debt driven endothelial damage and ATC might be considered collectively as “blood failure” due to the highly connected networks between these drivers.

This article presents the implications of oxygen debt for remote damage control resuscitation strategies, such as permissive hypotension and hemostatic resuscitation. We review the impact of whole blood resuscitation and red blood cell efficacy in mitigation of oxygen debt. At last, this article recognizes the need for simple and durable, lightweight equipment that can detect the adequacy of tissue DO2 and thus patient needs for resuscitative care.

Point-of-care lactate measuring may be a predictive tool for identifying high-risk trauma patients and occult shock because it provides information beyond that of vital signs and mechanism of injury as it may help predict the level of oxygen debt accumulation and need for resuscitation. Serial measurements may also be valuable as a tool in guiding resuscitative efforts.

INTRODUCTION

Almost 100 years ago, Robertson and Watson described the degenerative changes that take place in the organism when the exsanguinated condition persisted for more than a few hours.1 They recommended to be cautious with the use of saline and warned not to wait too long before resorting to blood transfusion to improve the chances of successful surgery and recovery. This apt description of hemorrhagic shock is no less relevant today where identification and treatment of hemorrhagic shock continues to represent a serious

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In a normal resting state, VO$_2$ is independent of DO$_2$. Or, in other terms, the whole body metabolic demand of oxygen consumption (VO$_2$) cannot meet tissue VO$_2$ (critical DO$_2$), VO$_2$ becomes directly dependent on DO$_2$ and anaerobic metabolism increases, leading to increasing levels of lactate. This signals the beginning of shock and the accumulation of oxygen deficit, the degree of which is determined by the magnitude of VO$_2$ below its aerobic threshold. The accumulated oxygen deficit over time is oxygen debt.

Fig. 1. Biphasic relationship between oxygen consumption (VO$_2$) and oxygen delivery (DO$_2$) (Solid line). As noted, DO$_2$ can vary widely without a drop in VO$_2$ as extraction of delivered oxygen can increase to continue to meet tissue VO$_2$ and thus lactate levels do not rise (Dashed line). However, when DO$_2$ drops to a point where extraction of delivered oxygen cannot meet tissue VO$_2$ (critical DO$_2$), VO$_2$ becomes directly dependent on DO$_2$ and anaerobic metabolism increases, leading to increasing levels of lactate. This signals the beginning of shock and the accumulation of oxygen deficit, the degree of which is determined by the magnitude of VO$_2$ below its aerobic threshold. The accumulated oxygen deficit over time is oxygen debt.

challenge in prehospital trauma care, especially when definitive care is delayed.

Robertson's and Watson's description of the exsanguinated condition over time encompasses the concept of oxygen debt, a well-known driver of survival from hemorrhagic shock and an increasingly recognized initiator and sustainer of important intermediary physiologic processes such as coagulopathy and inflammation. The fact that Robertson and Watson recommended early use of blood and less reliance on saline also recognizes and underscores the importance of developing strategies that limit the development of oxygen debt.

THE PHYSIOLOGY OF OXYGEN DEBT AND THE QUANTIFICATION OF SHOCK

Hemorrhagic shock is both a local and systemic disorder. In the context of systemic effects, blood loss may lead to levels of reduced oxygen delivery (DO$_2$) sufficient to cause tissue ischemia. Oxygen debt can be viewed as another term for whole body ischemia. While stroke and myocardial infarction are examples of ischemia in isolated organ systems, shock is the example for whole body ischemic events during hemorrhage. To understand the concept of oxygen debt, one must look at the biphasic relationship between the oxygen consumption (VO$_2$) and DO$_2$. In a normal resting state, VO$_2$ is independent of DO$_2$. Or, in other terms, the whole body metabolic demand of oxygen (VO$_2$) is not limited by the DO$_2$. The global DO$_2$ to the tissues can be derived from Fick's equation, where DO$_2$ is the product of cardiac output, hemoglobin oxygen saturation and the hemoglobin concentration. DO$_2$ at the tissue level is, of course, affected by other variables that can be adversely affected by low flow states, such as vasoregulation and capillary patency, making tissue DO$_2$ and its maintenance more complex.

As tissue DO$_2$ decreases through hemorrhage, compensation occurs through greater oxygen extraction at the level of microcirculation to meet tissue VO$_2$. However, when oxygen extraction is not enough to meet demand (tissue DO$_2$ falls below the tissue VO$_2$), an inflection point called critical DO$_2$ is reached (Fig. 1). This inflection point represents the transition from mass aerobic metabolism to mass anaerobic metabolism where VO$_2$ now becomes directly dependent on DO$_2$. This metabolic transition moves tissues into an ischemic state where oxygen deficit exists. Because there is a significant associated time dimension, shock cannot be fully evaluated by the deficit at any given time period (snapshot). The shock state should account for the deficit accumulated over time since the point of injury. The oxygen deficit accumulated over time is thus termed oxygen debt. As the DO$_2$/VO$_2$ ratio falls, a greater deficit accumulates, and when multiplied by time, a greater cumulative debt also accumulates. Thus shock and oxygen debt are synonymous, but with oxygen debt being a more quantitative descriptor of the state over time.

An often overlooked physiologic principle in regards to oxygen debt is the need for timely repayment of critical portions of this debt as soon as possible. Similar to other physiologic debts such as sleep, it is not possible to incur a significant oxygen debt and suffer no consequences for lack of timely repayment. It is simply not enough to stop incurring a deficit. So, in addition to restoring DO$_2$ to meet the basal metabolic demands of the body (on mean 200-250 cc/min), thus halting additional deficit accumulation, as much as 10 L of additional consumption may be required to replenish such critical cellular energetic processes as the phosphagen and glycogen-lactic acid system, which can be significantly depleted in shock. The ability to repay decreases with increasing levels of debt.

The accumulations of critical levels of oxygen debt and failure to repay in a timely manner have consequences. Rixen and others have shown a correlation between oxygen debt and the amount of reperfusion and inflammatory injury. Again, if we look at stroke or acute myocardial infarction (AMI), the greater the ischemic burden, the worse the tissue will do on reperfusion. Several pathophysiological mechanisms ranging from free radicals and oxidative damage, calcium influx, necrosis, and apoptosis lead to further multiorgan dysfunction syndrome (MODS). Capillary leakage will lead to activation and
infiltration of neutrophils into the parenchyma. As the gut starts leaking bacteria, endotoxins may enter the systemic circulation and initiate an aggregated inflammatory reaction. Much of the final organ damage and failure in the end will be due to irreversible mitochondrial damage.

The pathophysiological course of hemorrhagic shock is also reflected in mortality data. Current knowledge points at three cohorts in which death can be caused by either intractable rapid exsanguination, irreversible shock in the acute phase refractory to resuscitation measures (when oxygen debt proves lethal), or subacute MODS in patients who survive surgery and die in the ICU.7,8

While the linkage between oxygen debt and traditional organ failure (renal, hepatic, lung, etc.) has been long recognized, we should consider two additional linked and very dynamic tissues that are very sensitive to oxygen debt and are at risk for failing, having implications for all other organ systems. These two tissues, endothelium and blood, can be thought of as an integrated organ system, both from a developmental standpoint and from the perspective of shock. The microcirculation with its endothelial lining is estimated to represent an area of 4000-7000 m² and thus might be considered, along with the blood it envelops, the body’s largest integrated functional organ system. With over 10¹³ cells, the endothelium is a major target of damage from trauma, hemorrhage, hypoperfusion, and reperfusion injury. Recent attention to the endothelium’s glycocalyx structure and function are now providing important insights into its role in the development of response to trauma.⁹

The degree of damage to the endothelium is largely modulated by the degree of hypoperfusion experienced, which is believed to begin a cascade of events leading to acute traumatic coagulopathy (ATC). ATC is characterized by a systemic combination of fibrinolysis and to some extent anticoagulation driven by the protein C pathway. Platelet dysfunction also occurs through mechanisms that have yet to be fully elucidated. Evidence indicates that the degree of hypoperfusion and resulting oxygen debt is the main driver behind ATC and that significant coagulopathy can occur before fluid resuscitation.² New evidence indicates that reperfusion injury may damage fibrinogen and fibrin, thus making for weaker clots and further exacerbating ATC.¹⁰ Further blood loss, crystalloid-induced hemodilution, acidosis, hypothermia, occurring during the course of continued hemorrhage and treatment only serve to exacerbate ATC, creating conditions favorable for more bleeding and worsening of oxygen debt. This combination of oxygen debt-driven endothelial damage and ATC might be considered collectively as “blood failure” due to the highly connected networks between these drivers.

Both animal and clinical data support that late outcome is correlated with the severity and duration of shock, and that metabolic correlates are the best predictors of outcome. This is why mitigation of oxygen debt accumulation and oxygen debt repayment should be a primary goal in prehospital trauma care. Resuscitation guidelines and strategies should adopt these principles to develop logical strategies that optimize outcomes in the challenging prehospital care environment.

THE GREAT CHALLENGE OF AVOIDING BLOOD FAILURE: OXYGEN DEBT AND REMOTE DAMAGE CONTROL RESUSCITATION

Remote damage control resuscitation (RDCR) is a treatment strategy for the severely injured trauma patient designed to limit hemorrhage and to produce or preserve an adequate level of physiologic reserve to deliver a patient that can be salvaged with the follow-on strategy of damage control surgery.¹¹ Since definitive control of hemorrhage can rarely be guaranteed in the prehospital setting, the doctrine of permissive hypotension has been adopted as a strategy for RDCR to limit ongoing hemorrhage by reducing hydrostatic pressure while maintaining a “critical level” of vital organ perfusion. The practice is, in theory, an overall component of hemostatic resuscitation. This strategy is not new. In 1945, Emerson suggested an approach to combat casualties in hemorrhagic shock using resuscitation that avoids excessive hemodilution with plasma (not more than 1000 cc) and restoring the systolic pressure to 100 mmHg before surgery. This approach, based on whole blood (WB) and plasma only, allowed a slightly higher pressure and thus a higher flow and DO₂.¹² Very general physiologic parameters have been suggested to guide permissive hypotension, such as maintenance of a palpable radial pulse, mental status, and an systolic blood pressure (SBP) of 80-100 mmHg. Recently, Eastridge et al. published data suggesting that an SBP of 100 mmHg should define hypotension and impending hypoperfusion, at least for the battlefield casualty.¹³ Systolic blood pressures below 100 mmHg were associated with increased base deficits (indicating greater oxygen debts) and mortality. Data are lacking to support the use of other physical resuscitative endpoints such as a palpable radial pulse or mental status.

There are, of course, many challenges to the use of permissive hypotension, including the desire to titrate blood pressure to a level that limits hemorrhage but at the same time halts the continued accumulation of oxygen debt. Obviously, factors such as prolonged transport times, limited monitoring tools, and limited availability of blood products make widespread and precise adoption of such strategies very complicated. In this context, and according to Fick’s equation, resuscitation with clear fluids to increase cardiac output to sustain adequate DO₂ will lead to dilution of hemoglobin levels. Over time, and following repeated boluses, this will leave the patient in a downward spiral in relation to DO₂. Thus, early transfusion of erythrocytes is
This approach represents the best chance to avoid or correct blood failure and its underlying drivers. Recent data demonstrating the endothelium-restoring capacity of plasma, for example, help to underscore that the benefit of all products together are greater than the sum of their parts. However, implementing such strategies far-forward where they would have their greatest benefit is logistically challenging. The ideal approach may be to consider a wider use of WB.

A mixture of red blood cells (RBCs):plasma:platelets in a 1:1:1 ratio contains a hemoglobin concentration of around 9 g/dL due to the anticoagulants and RBC additive solutions. WB (approximately 450 mL blood + 63 mL preservation solution) has a mean hematocrit of 40%-45%, which gives a mean hemoglobin level of 13-14 g/dL (using healthy young individuals as donors). According to Fick's equation, the WB approach gives a DO$_2$ 30% higher than the component approach in a volume replacement transfusion. This may be crucial for mitigating oxygen debt during ongoing bleeding and delayed evacuation. Furthermore, the practical resuscitative efforts in the context of workload should be easier with the WB approach compared to 1:1:1 therapy, simply because it is easier to transfuse one bag instead of three.

Fibrinogen levels should also be taken into consideration. With the 1:1:1 component approach, the patient will soon reach a critical fibrinogen level due to low levels in freeze dried and fresh frozen plasma, and extra fibrinogen concentrate must be considered. WB fibrinogen levels from healthy young donors levels mean about 3 g/L, mitigating fibrinogen depletion in the patient during ongoing bleeding.

The impact of the platelet contribution from WB resuscitation in the preshospital setting also has to be evaluated because there exist clinical studies showing improved survival with early use of platelets in combination with RBCs and plasma. The current Tactical Combat Casualty Care (TCCC) guidelines now recommend WB as the number one preferred fluid for hemorrhagic shock resuscitation in combat casualties. Mitigating oxygen debt with WB may be superior to component therapy and easier to implement than initially believed. Both cold-stored WB, and warm fresh WB drawn from a walking donor pool or an emergency donor panel are feasible. Simple use of RBC units (discussed below) does not represent an adequate solution to the problem.
shock. It is commonly believed that because transfused RBC units increase hemoglobin content and blood oxygen content, that DO₂ to tissue is likewise improved. Some data suggest, however, that with increasing storage duration, DO₂ may be in fact progressively impaired by altered oxygen affinity, unfavorable rheology and adhesion, as well as by abnormal vascular signaling by RBCs that increases regional vascular resistance (and diminishes regional blood flow despite adequate perfusion pressure).23 This is of particular concern because these RBC storage lesions are generally believed to increase over time and are coupled with the routine practice of transfusing the oldest units from the blood bank into trauma patients.24

Recent large RCTs in nontrauma patients have not indicated a clinical benefit from the use of “fresher” RBCs.25-27 These trials, however, were in critically ill patients that were not in hemorrhagic shock, which limits their generalizability to this population. In addition, there is increasing awareness that donor variability in RBC quality is high. This donor variability in RBC quality causes the stored RBCs to “age” differently, and as a result the use of RBC age as a measure of quality may not be accurate.28 Investigators are examining whether there are other RBC quality measures that can be used as more accurate surrogates for RBC quality.

Clinicians need to appreciate that native RBC function in increasing DO₂ may be altered or diminished in stored RBC-containing blood products. There are in vitro, animal, and nonrandomized studies in adult trauma patients that indicate that RBCs of increased storage duration are associated with reduced DO₂, reduced perfusion, and perturbed vasoregulation, as well as impaired immune and coagulation function.29-31 A recent study by Kiraly and colleagues in adult trauma patients indicated that RBCs stored for more than 21 days reduced DO₂ compared with those stored for less than 21 days.31 Another prospective study performed in a severe pneumonia model in canines indicated that transfusion of older RBCs was associated with impaired vasoregulation and increased mortality.32 With the preponderance of animal and human data indicating reduced efficacy and safety of older RBCs in critically ill populations, particularly in trauma patients, it is appropriate, if possible, to preferentially use RBCs or WB of reduced storage duration (<15 days) until there is evidence that older RBCs are equivalent to fresher ones. If fresher RBCs are not available, it is still important to transfuse available RBC or WB units because impaired regulation of regional blood flow is a moot point if overall cardiac output and hemodynamics are inadequate to generate regional perfusion pressure. Also, if the patient survives the acute resuscitation, some of the adverse effects associated with the storage lesion appear to reverse in the 48 hours following transfusion, such as loss of 2,3-DPG and ATP concentrations (e.g., akin to improved function of transplanted organs over time).33

Human trials are needed to evaluate the efficacy of RBCs to reverse shock in patients with traumatic hemorrhagic shock. Clinical measures of efficacy in future trauma trials can be measured, such as improvement in lactate concentrations, tissue DO₂ and consumption, functional hemostatic measures, organ function, and other morbidity measures, as well as mortality.

MONITORING: THE MISSING LINK

Identification, quantification, and monitoring of shock represent the greatest clinical challenges in the treatment of traumatic shock, especially in the prehospital setting. In this phase, decisions are largely based on recognition of the mechanism of injury and clinical evaluation of vital signs. Occult shock (shock in the presence of a normal range of vital signs, or accumulating oxygen debt) is a significant problem because healthy young individuals have great compensatory reserves. Resuscitation decisions are based on uncertainty regarding the anatomic source of bleeding and the volume and duration of hemorrhage. In part due to the lack of advanced diagnostic tools in the field, management of shock is a difficult task even for the most experienced of clinicians. In the combat theatre, one also has to remember that most front-line providers have medical care as a secondary task. Senior policymakers attempt to compensate for this by developing and relying on protocols to overcome this gap.

Many protocols rely solely on systolic blood pressure, heart rate, and mental status, despite the fact that none of these are optimal surrogates for cellular perfusion. Prospective research suggests that while casualties with hypotension have greater base deficits and mortality, these measures lack specificity that would optimize the use of therapeutic resources to significantly improve outcomes.3,4,34,35 In this context, there is an obvious need for simple and durable, lightweight equipment that can detect the adequacy of tissue DO₂ and thus patient needs for resuscitative care.

Given the importance of addressing the development of oxygen debt, the ability to leverage a metabolic signal to identify, track, and guide therapy to reduce oxygen debt should be desirable. To this end, the use of lactate monitoring is attractive. Many studies have correlated lactate levels in trauma to outcomes, including its measurement in the prehospital setting.36-38 Guyette et al. found that lactate is superior to other early surrogates of hypoperfusion (systolic blood pressure and shock index) in predicting the need for resuscitative care in trauma patients presenting with a systolic blood pressure between 70 and 100 mmHg.39 The linkage of lactate levels to base deficit values as indicative of hypoperfusion (oxygen debt) and development of ATC also underscores its potential value.
Studies have demonstrated the ability of serial lactate levels to quantify oxygen debt and even identify an LD50 in animals.\(^\text{A0}\) Given these data and the availability of small, lightweight point-of-care lactate (P-Lac) devices, the use of serial field lactate monitoring may serve as a valuable tool in guiding RDCR and in optimizing scarce resources such as the use of WB.

Thus P-Lac may be a predictive tool for identifying high-risk trauma patients and occult shock because it provides information beyond that of vital signs and mechanism of injury, predicting the level of oxygen debt accumulation and need for resuscitation. An isolated lactate measurement above 4-5 mmol/L has been demonstrated to predict the need for resuscitative care.\(^\text{A9}\) Furthermore, trends in lactate levels such as lactate clearance will be useful in understanding the true effectiveness of resuscitation even in patients with normal vital signs.

A few caveats and possibilities should be noted to maximally leverage P-Lac monitoring. First, serial measures and not singular measures are most important. It is the degree of lactate elevation over time that will be most valuable in understanding an individual’s accumulating oxygen debt, position on the DO\(_2\)/VO\(_2\) curve, likely outcomes, and optimal therapy. Monitoring P-Lac every 30-60 minutes is recommended as a strategy to guide therapy. It is difficult to overstate the potential value of this, especially if multiple casualties are encountered and resources such as blood products are scarce and evacuation times are prolonged. For example, a casualty with a persistently elevated lactate above 10 mEq/L for 2-3 hours might not be considered a candidate for additional blood products, because the accumulated oxygen debt is likely not consistent with survival.\(^\text{A0}\)

A second important caveat is that while lactate clearance in the hemorrhaging casualty is a sign that the continued accumulation of oxygen debt has been halted, it is not an indication that oxygen debt has been repaid to any significant extent. The reason for this can be seen in Fig. 1. Due to the biphasic nature of the relationship between DO\(_2\) and VO\(_2\), DO\(_2\) can be pushed up just past the point of DO\(_{2\text{crit}}\) where VO\(_2\) is not DO\(_2\) dependent. At this stage, anaerobic metabolism has shifted to aerobic metabolism, and lactate production is reduced. The previously produced lactate will be metabolized by the liver and kidney. However, one cannot know if debt has been adequately repaid. Thus, while lactate monitoring can be used to quantify accumulating debt, it is a poor guide in debt repayment. There are currently no technologies available in or out of hospital that can be used in a practical sense to know if debt is being or has been adequately repaid. It should also be stressed that moving the casualty to a state of VO\(_2\) that is independent of DO\(_2\) to halt the accumulation of oxygen debt is not to be confused with resuscitating to supranormal levels of DO\(_2\). The practice of driving DO\(_2\) to supranormal levels has been associated with adverse events such as overresuscitation, leading to abdominal compartment syndrome and other complications.\(^\text{A1}\)

Lastly, casualties who are physically active before injury may have significantly elevated lactate levels initially, since oxygen debt can be incurred through strenuous activity. However, hyperlactatemia from this alone should clear rapidly. Persistently elevated lactate levels, especially after transfusion, would indicate oxygen debt from hemorrhage.

### A MORE PERSONALIZED AND PRECISE APPROACH TO RDCR

Based on the facts discussed above, we propose a more personalized and precise approach to RDCR, using a combination of mechanism of injury, SBP tracking, and P-Lac monitoring in triage as well as in monitoring resuscitative efforts. Mechanism of injury may be the most important initial trigger for resuscitative care in the field. This notion has been supported by Benfield et al., who showed an association between the pattern of injury and the total number of blood products needed for resuscitation.\(^\text{A2}\) However, we must be cognizant of the need for additional triggers to either continue or modify resuscitations because of the resource limitations imposed by RDCR. We thus recommend mechanism of injury as a primary decision-making foundation. Together with trending lactate and SBP, enough parameters may be available to develop a logical approach to a more personalized RDCR that limits oxygen debt, avoids blood failure and maximizes utilization of resources.\(^\text{A3}\) For example, an SBP of 90 mmHg in the face of lactate clearing in one individual would pose different resource allocation and ongoing resuscitation strategy options than an SBP of 110 in an individual with a climbing lactate.

### CONCLUSION

Because of its essential role in survival and resuscitative complications, mitigation of oxygen debt accumulation in the prehospital phase is imperative to reduce the incidence of blood failure and improve outcome in hemorrhagic shock. Ideally, this should be accomplished by rapid, aggressive hemorrhage control when possible, followed by a resuscitation strategy based on blood products. WB is the preferred product in optimizing DO\(_2\) to a point proximal to critical DO\(_2\) sufficient to support tissue VO\(_2\) in a delivery independent manner, thereby halting the accumulation of oxygen debt. Permissive hypotension has to be further evaluated in the context of oxygen debt accumulation, especially in the case of delayed evacuation. After surgical hemorrhage control, repayment of debt should occur as quickly as possible.
Today, prehospital care providers are challenged to perform under extreme conditions. There is a “gap” where providers, sometimes with medical care as a secondary task, have to carry out advanced resuscitation procedures with minimal equipment and limited experience. This gap must be filled with reliable, simple protocols and procedures focusing on the principles of oxygen debt repayment and thus mitigation of blood failure. Use of tools such as P-Lac monitoring in combination of monitoring of SBP could bring tremendous value in guiding RDCR and leveraging permissive hypotension as a hemostatic strategy. Lastly, it is also important to remember that management recommendations are guidelines rather than definitive standards of care.

CONFLICT OF INTEREST
The authors have disclosed no conflicts of interest.

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