Minireview

Physiological comparison of hemorrhagic shock and $\dot{V}O_2$max: A conceptual framework for defining the limitation of oxygen delivery

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Impact statement

Disturbance of normal homeostasis occurs when oxygen delivery and energy stores to the body's tissues fail to meet the energy requirement of cells. The work submitted in this review is important because it advances the understanding of inadequate oxygen delivery as it relates to early diagnosis and treatment of circulatory shock and its relationship to disturbance of normal functioning of cellular metabolism in life-threatening conditions of hemorrhage. We explored data from the clinical and exercise literature to construct for the first time a conceptual framework for defining the limitation of inadequate delivery of oxygen by comparing the physiology of hemorrhagic shock caused by severe blood loss to maximal oxygen uptake induced by intense physical exercise. We also provide a translational framework in which understanding the fundamental relationship between the body's reserve to compensate for conditions of inadequate oxygen delivery as a limiting factor to $\dot{V}O_2$max helps to re-evaluate paradigms of triage for improved monitoring of accurate resuscitation in patients suffering from hemorrhagic shock.

Abstract

Based on evidence extracted from a cross-sectional review of the literature, we sought to advance a novel conceptual framework that the physiology of hemorrhagic shock from exsanguination and maximal oxygen uptake ($\dot{V}O_2$max), induced by physical exercise, shares key common features. As such, this review focuses on the notion that intolerance to inadequate oxygen delivery (DO_2) resulting from associated states of hypovolemia appears to be a common physiological link that "connects" hemorrhagic shock to the physiology that limits maximal aerobic capacity. Our approach focuses on the similarities in a complex cascade of cardiopulmonary, metabolic and autonomic compensatory responses during hemorrhage and maximal physical exertion that ultimately function to avoid critical levels of DO_2 (DO_{2crit}) and are manifested by elevation in blood lactate levels. We introduce a paradigm of absolute (i.e. hemorrhage) versus relative (i.e. exercise) hypovolemia as a primary physiological factor that contributes to reaching DO_{2crit}, and define the concept of "O_2 deficit" to replace the clinical concept of O_2 debt. Using the peer-reviewed literature, we provide human data obtained from patients who suffered hemorrhagic shock from severe blood loss and compare it to healthy subjects who performed maximal exercise. We include a novel conceptual framework of the continuum of metabolic relationship between DO_2 and $\dot{V}O_2$ that is manifested as the final step during both progressive blood loss leading to hemorrhagic shock and at $\dot{V}O_2$max. We present evidence to support the contribution of utilizing "O_2 extraction reserve" as the initial mechanism for developing an O_2 deficit, and the notion of individual variability in compensatory responses. In the absence of reversing inadequate DO_2, an increased reliance on O_2 extraction reserve, cellular anaerobic glycolysis, and phosphocreatine stores to supplement the energy required by the tissues for normal function will deplete a finite capacity for compensation. In the end, acidity reflected by a blood pH $\leq \sim$7.0 leads to disturbance of normal cell functioning of metabolic machinery manifested by irreversible shock in the case of hemorrhage or physical exhaustion when $\dot{V}O_2$max is reached.

Keywords: Oxygen deficit, oxygen extraction reserve, blood pH, blood lactate, compensatory reserve

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Introduction

Maintaining a balance between delivery and utilization of oxygen in various organs of the body represents a fundamental premise for sustaining "adequate" tissue oxygenation and cell function. As the requirement for oxygen uptake and utilization ($\dot{V}O_2$) to meet cellular energy demand overwhelms the capacity of the respiratory and circulatory systems to deliver oxygen (DO_2), the cells must rely increasingly on the metabolic transformation of glycogen to lactate known as anaerobic glycolysis, as well as tissue oxygen and phosphocreatine stores. Systemic DO_2 is the product of cardiac output and arterial oxygen content.[1] Mitigating the potential impact of failure to maintain an adequate DO_2 on disrupting normal metabolic functioning at the cellular level relies on the integration of numerous compensatory mechanisms.

"Shock" has been described as a pathophysiological condition of "inadequate tissue oxygenation"[1,2] that ensues when DO_2 fails to meet the tissue $\dot{V}O_2$ required to maintain aerobic energy production.[2,3] In the context of this definition, maximal intensity exercise could be described as a type of "shock" in individuals, including endurance-trained athletes, whose $\dot{V}O_2$max is limited by a failure of DO_2 to meet the energy demand of working muscles.[4–8] Within this context, progression of tissue acidity indicates failure to sustain a balance in oxygen supply and cellular energy demand that underlies the onset of both hemorrhagic shock and $\dot{V}O_2$max. Although the magnitude of compensatory responses can differ between these two physiological states, we recognize that both hemorrhagic shock and $\dot{V}O_2$max display qualitatively many similar hemodynamic, autonomic, metabolic, and compensatory patterns. Figure 1 represents our conceptual framework to illustrate the cascade coupling of ventilation, circulation, tissue metabolism, and energy balance in the mitochondria. Within this construct, an inability to maintain adequate DO_2 to the cells can lead to disturbance of normal cellular metabolic functioning that defines a common pathway in both hemorrhagic shock and $\dot{V}O_2$max. In this mini-review, we used this model in the context of young healthy humans, trained fit individuals, and/or athletes where, in general, DO_2 sets the upper limit for $\dot{V}O_2$max. Our primary comparison population from a conceptual perspective is young trauma victims, especially battlefield casualties. Our index populations are generally similar, so we explored relevant literature in an attempt to gain insight about the limiting factors that lead to hemorrhagic shock in bleeding patients by comparing the pathophysiological mechanisms of exsanguination to the physiological limits of individuals whose $\dot{V}O_2$max is limited by inadequate DO_2.

Absolute vs. relative hypovolemia

Central hypovolemia represents another common fundamental physiological state that underlies the inadequate DO_2 resulting from both hemorrhage and many instances of physical exertion at $\dot{V}O_2$max. Hypovolemia is defined as a reduction in circulating blood volume relative to the capacitance of the cardiovascular space. Figure 2 provides an illustration of the difference in the hypovolemic state caused by hemorrhage from that resulting from an acute exercise. During hemorrhage, an "absolute" hypovolemia occurs as a consequence of reduced circulating blood volume within the same vascular space (or smaller as ongoing compensatory vasoconstriction occurs).[10,11] In contrast, increased vascular capacitance due to significant vasodilation in working muscles during acute exercise results in a "relative" hypovolemia defined by vascular space expansion with no or negligible change in circulating volume.[10,11] Consequently, we can think of assessing limitations in compensatory adjustments to hemorrhage and $\dot{V}O_2$max in DO_2-limited individuals as a comparison in physiological differences in DO_2 associated with absolute and relative hypovolemic conditions that eventually lead to underperfused tissue.

Clinical concepts of oxygen deficit and debt

The terms oxygen "deficit" and or "debt" are routinely used in emergency and critical care medicine to reflect a mismatch between cellular energy requirement and $\dot{V}O_2$.[2,12–14] The conceptual use of the terms O_2 deficit or debt by clinicians can be linked to the concept of a cumulative deficiency of DO_2 needed to support cellular energy demands through oxidative metabolism that was initially described by A.V. Hill from experiments using strenuous physical activity performed by healthy individuals.[15] Hill's research included the measurement of $\dot{V}O_2$ responses during steady-state and maximal exercise, laying the

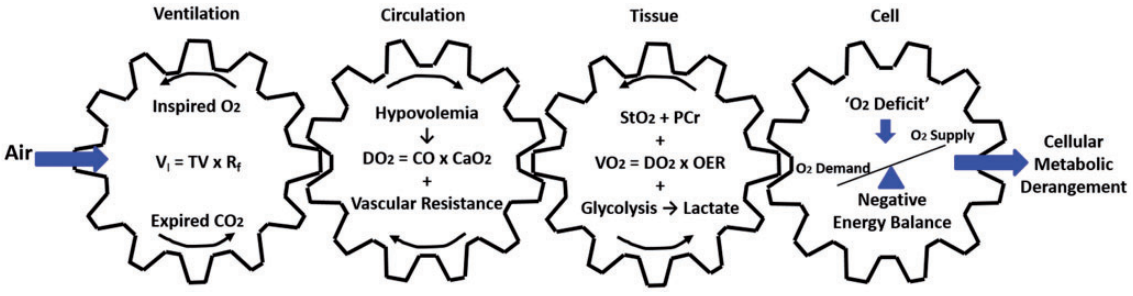

Figure 1. Conceptual model to illustrate the cascade coupling of ventilation, circulation, tissue metabolism, and energy balance in the mitochondria to cell function that defines common pathways to hemorrhagic shock and VO_2max. VI: inspiratory volume; TV: tidal volume; Rf: respiratory frequency; DO_2: oxygen delivery; CO: cardiac output; CaO_2: oxygen carrying capacity; VO_2: oxygen uptake; OER: oxygen extraction ratio; StO_2: tissue oxygen saturation; PCr: phosphocreatine. Conceptually adopted from Wasserman.[9] (A color version of this figure is available in the online journal.)

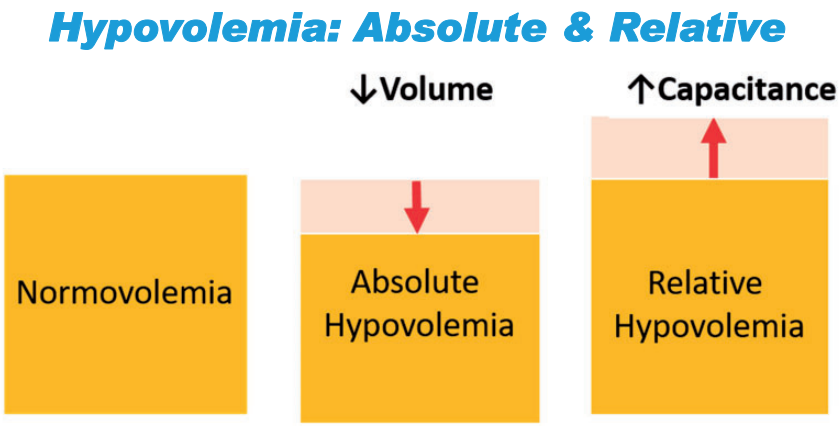

Figure 2. Conceptual comparison of normal circulating blood volume (normovolemia) with absolute and relative hypovolemia. Orange indicates circulating blood volume; Pink indicates capacitance of vascular space. Adopted from M.N. Sawka with permission. (A color version of this figure is available in the online journal.)

foundation for defining systemic $\dot{V}O_2$ dynamics and the emergence of the concepts of O_2 deficit and O_2 debt.[15] Subsequently, O_2 deficit and or O_2 debt have been used repeatedly in the clinical literature to describe the ultimate pathophysiological factor leading to shock.[2,12,13,16] However, the use of "O_2 debt" can be misleading and confusing to physiologists who recognize it as referring to a post-exercise $\dot{V}O_2$ phenomenon that is quantitatively and physiologically different than O_2 deficit.[17,18] In an effort to alleviate confusion in terminology between clinicians and physiologists, we will use the term O_2 deficit as a more appropriate term to describe cellular $\dot{V}O_2$-energy requirement mismatch and "O_2 extraction reserve" to reflect various sources of O_2 available to cells to support their energy requirements (e.g. hemoglobin, myoglobin). Within this context, it is conceptually transparent that reduced total O_2 availability resulting from lowered DO_2 during severe blood loss or $\dot{V}O_2$max will result in increased O_2 deficit because O_2 is "barrowed" from the O_2 extraction reserve. Thus, O_2 deficit represents a mechanism of compensation designed to avoid reaching the DO_2crit. As such, we use this review to focus on lowered DO_2 as the underpinning of progressive reduction in O_2 extraction reserve in an effort to support increased O_2 deficit that leads to failure in meeting cellular energy demands during either hemorrhagic shock (absolute hypovolemia) or $\dot{V}O_2$max (relative hypovolemia).

Inadequate DO_2 created by $\dot{V}O_2$max. Inadequate DO_2 can be defined as inability of O_2 delivery to tissues to meet cellular energy demand. Figure 3 provides a conceptual schematic of the continuum of DO_2 moving from normal rest. Moving to the right of resting baseline $\dot{V}O_2$ (yellow bar in Figure 3) with the initiation of physical exercise, DO_2 is progressively increased as a result of increased systemic blood flow (cardiac output). Despite higher absolute DO_2 during exercise, there is an immediate development of an O_2 deficit due to the time delay between immediate energy requirement and systemic $\dot{V}O_2$. It is noteworthy that during the mismatch between energy requirement and $\dot{V}O_2$ in the working muscle, blood lactate usually does not appear until the individual reaches a physiological work capacity above ~50% of $\dot{V}O_2$max.[19] As such, an O_2 deficit during physical exertion is initiated by two compensatory mechanisms that work in concert to mobilize O_2 from the O_2 extraction reserve in the presence of inadequate DO_2: (1) increased extraction of hemoglobin-bound oxygen delivered through increased blood flow to the tissue (i.e. higher oxygen extraction ratio, OER in Figure 3) with a subsequent reduction in measured oxygen saturation of venous blood (SvO_2); and (2) utilization of local tissue and O_2 bound to myoglobin (SmO_2) in addition to reserves of phosphocreatine (PCr) (Figure 3, right pink area).[20] When increased DO_2 and utilization of PCr/O_2 reserves fail to support the cellular energy requirement, DO_{2crit} is reached resulting in the production of energy through initiation of the transformation of glucose or glycogen to lactate. With limited amounts of oxygen available for aerobic glycolysis, an accumulation of lactate gradually appears in the blood in the presence of inadequate lactate clearance.[4,21,22] When increasing energy demand can no longer be supported in the presence of accumulated O_2 deficit, physical exhaustion is manifested by reaching $\dot{V}O_2$max. In the end, the prevailing evidence indicates that $\dot{V}O_2$max in healthy exercising humans is ultimately limited by inadequate DO_2.[4,23]

Inadequate DO_2 created by hemorrhage. The extrapolation of metabolic events that lead to $\dot{V}O_2$max induced by intense physical exercise to severe blood loss is reflected by a final common pathway that an inadequate DO_2 limits tolerance of the body's organs to sustain cellular energy requirements after reaching DO_{2crit}. Similar to inadequate DO_2 that limits the healthy exerciser from performing more physical work beyond $\dot{V}O_2$max, is the arrival at a threshold of intolerable reduction in O_2 extraction reserve with blood loss. This is due to the reduced DO_2 that is not restored over time, which will lead to irreversible shock and death.[13,14] Moving to the left from resting baseline $\dot{V}O_2$ along the continuum with the initiation of hemorrhage (Figure 3), DO_2 is reduced as a result of a loss of oxygen-carrying red blood cells and lower circulating volume for cardiac filling and output. Despite the progressive reduction in DO_2 during the early stages of bleeding, $\dot{V}O_2$ can be maintained at

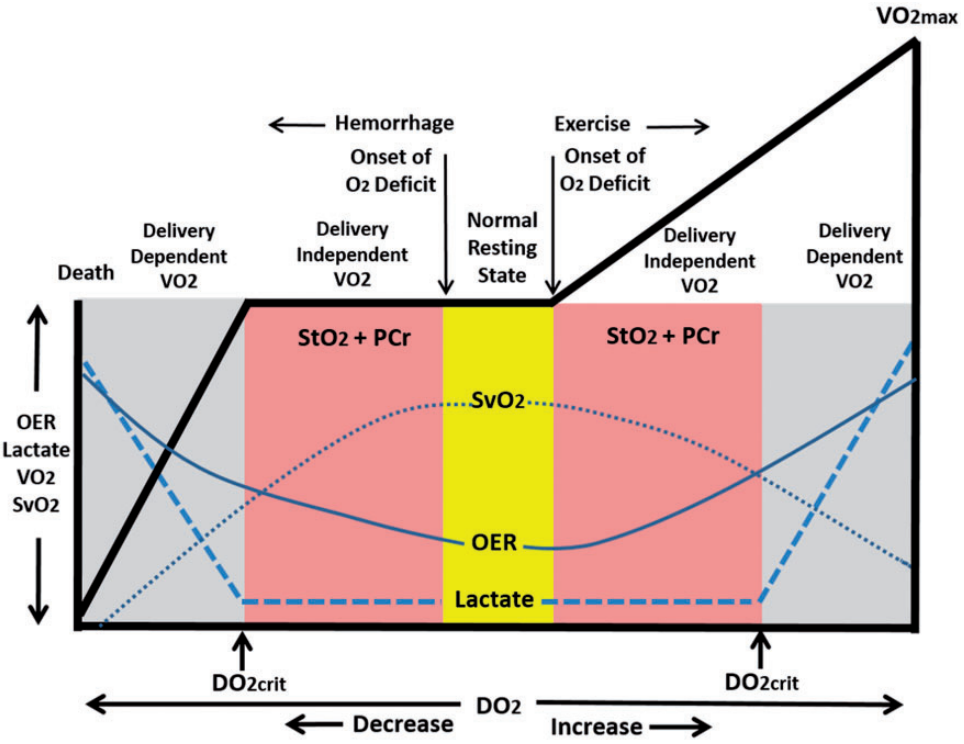

Figure 3. Conceptual representation of the continuum of metabolic relationship of oxygen delivery (DO_2) to utilization (VO_2) responses from hemorrhagic shock (left of Normal Resting State) to exertion at VO_2max (right of Normal Resting State). OER: oxygen extraction ratio; SvO_2: venous oxygen saturation; StO_2: tissue oxygen saturation; PCr: phosphocreatine; DO_{2crit}: critical oxygen delivery. Responses to progressive hemorrhage modified from Hooper *et al*.[13] See text for explanations.

baseline levels by the capacity to utilize the O_2 extraction reserve (i.e. increased OER); a cascade of events that is reflected by lowered SvO_2. This notion of an early delivery-independent $\dot{V}O_2$ in the presence of reduced DO_2 was best illustrated by Weiskopf *et al*.[24] who demonstrated no change in $\dot{V}O_2$ or blood lactate (i.e. failed to reach DO_{2crit}) following an experimentally-induced reduction in hemoglobin concentration (i.e. >60% lower DO_2). Like the condition of physical exercise, it might be expected that the cells can draw upon tissue PCr and O_2 extraction reserves (i.e. O_2 deficit) during hemorrhage. If O_2 extraction reserves contribute to the initial burden of an O_2 deficit during the delivery-independent $\dot{V}O_2$ phase of hemorrhage, higher O_2 extraction (OER) and lower tissue O_2 saturation (StO_2) would be expected before an appearance of lactate in the blood. Consistent with this hypothesis is an immediate and progressive reduction in StO_2 and elevation in OER during simulated human hemorrhage (Figure 4) while blood lactate remained within baseline levels (0.95 to 1.1 mmol/l) during lowered DO_2.[26]

Within this construct of timing, the clinical description of an onset of O_2 deficit as the point in time at which tissue metabolism converts to anaerobic glycolysis to produce lactate in an effort to sustain the total energy requirement of the cell during hemorrhage has been misleading.[1,13,14] Contrary to this hypothesis, failure to reach DO_{2crit} in the presence of reduced O_2 extraction reserves (Figure 4) supports the concept that O_2 deficit, defined by reduced O_2 extraction reserve, must occur in advance of reaching DO_{2crit}. As such, the onset of O_2 deficit during hemorrhage, like exercise, is initiated by a compensatory utilization of the O_2 extraction reserves before there is increased anaerobic glycolysis. As such, we propose a revision in the biphasic relationship between DO_2 and $\dot{V}O_2$[13] to include stores of tissue PCr and O_2 extraction reserve prior to the appearance of lactate in the blood (i.e. DO_{2crit}; Figure 3, left pink area). In the end, the burden of a cellular O_2 deficit beyond DO_{2crit} must be "repaid" to restore adequate metabolic function and prevent organ dysfunction or injury at the cellular level whether describing DO_2-limited strenuous physical activity that requires working at $\dot{V}O_2$max or life-threatening exsanguination.

Physiologic similarities between hemorrhagic shock and $\dot{V}O_2$max

The ultimate challenge of the cardiopulmonary and metabolic systems in both conditions of hemorrhagic shock and $\dot{V}O_2$max is to maintain a sustainable DO_2 so that a threshold of intolerable cellular O_2 deficit and disturbance of normal cell functional metabolism can be avoided. This challenge requires a physiological capacity to recruit a complex network of compensatory mechanisms with the ultimate function of defending against inadequate DO_2. A summary of compensatory responses and their outcomes is presented in Table 1 and described below.[27,28]

Hemodynamic mechanisms. Despite stark differences in systemic arterial blood flow, blood pressure, DO_2, and $\dot{V}O_2$, one of the most obvious features between exercise and

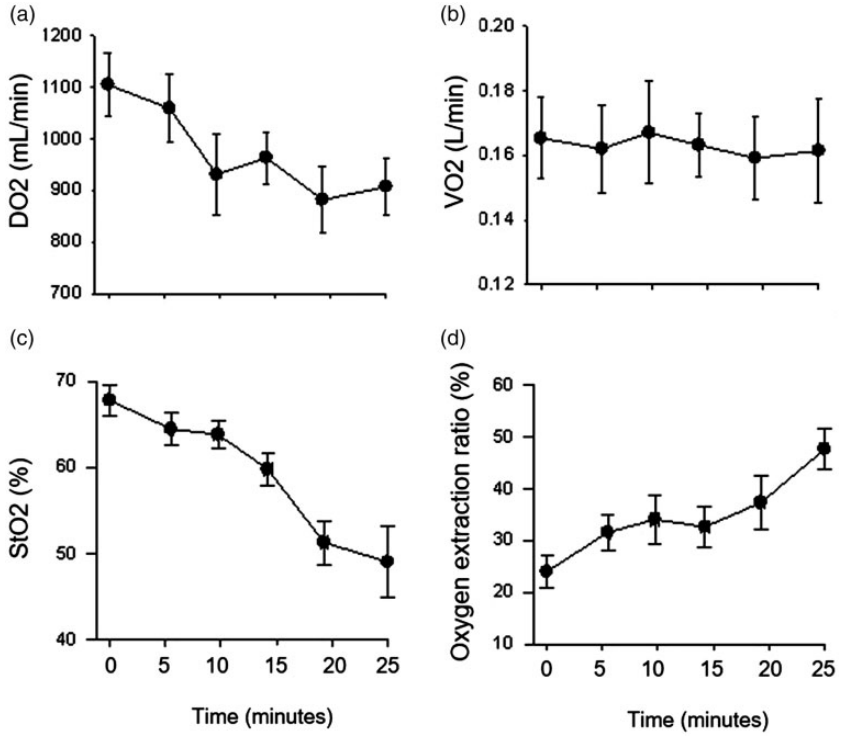

Figure 4. Time course of responses of systemic oxygen delivery (DO_2; Panel A), systemic oxygen uptake (VO_2; Panel B), tissue oxygen saturation (StO_2; Panel C), and oxygen extraction ratio (Panel D) during progressive central hypovolemia induced by lower body negative pressure (LBNP). Data are means ± SD; $n = 18$. Modified from Ward *et al*.[25]

Table 1. Similarities in qualitative and quantitative cardiopulmonary, metabolic and autonomic responses for hemorrhagic shock and exertion at $\dot{V}O_2$max.

Physiological responses	Directional change	Baseline rest	Hemorrhagic shock	References	Exertion @ VO_2max	References
O_2 deficit, mL kg^{-1} VO_2	↑	0	104[a]	Siegel *et al*.[16]	50–80	Linnarsson *et al*. [20] Joyner and Coyle [19]
StO_2, %	↓	75	29–50	Convertino and Sawka[10]	29–44	Martin *et al*. [29]
PtO_2, mmHg	↓	~34	5	McKinley *et al*.[30b]	3	Richardson *et al*.[31]
Heart rate, bpm	↑	60–70	120–180	Cloutier *et al*.[32] Gutierrez *et al*.[1]	140–200	Joyner and Casey[33] Tanaka *et al*. [34]
SNA, pg/mL	↑	200–500	5–10 fold	Woolf [35]	> 7-fold	Engelke and Convertino [36]
OER, %	↑	20–30	> 50	Ward *et al*. [25]	85–90	Joyner and Casey[33] Bassett and Howley[23]
SvO_2, %	↓	65–75	< 30	Kasnitz *et al*. [37]	< 20	Mortensen *et al*. [38]
Blood pH	↓	7.4	≥ 7.0	Cloutier *et al*. [32]	≥ 7.0	Osnes and Hermansen [39] Goodwin *et al*.[40]
Blood [LA], mmol/l	↑	1–2	> 3–13	Bonanno *et al*. [41] Vitek *et al*.[27]	15–25	Osnes and Hermansen [39] Ferguson *et al*.[4]
Blood BD, mmol/l	↑	0	> 5–15	Eastridge *et al*. [42]	~ 7	Osnes and Hermansen [39]
R_f, breaths/min	↑	10–20	> 35	Gutierrez *et al*.[1]	> 40	Forster *et al*. [43]
V_t, liters	↑	0.5	> 0.7	Convertino *et al*.[44]	> 2.5	Forster *et al*. [43] Younes and Burkes [45]
$EtCO_2$, mmHg	↓	35–40	< 35	Stone *et al*.[46] McManus *et al*.[28]	< 35	Hagberg *et al*. [47]
Compensatory Reserve, %	↓	90–100	< 15	Convertino *et al*. [48]	< 20	Convertino and Sawka [10]

StO_2: tissue oxygen saturation; PtO_2: partial pressure of tissue oxygen; SNA: sympathetic nerve activity; OER: oxygen extraction ratio; SvO_2: venous oxygen saturation; [LA]: lactate concentration; BD: base deficit; R_f: respiration frequency; V_t: tidal volume; $EtCO_2$: end-tidal carbon dioxide.
[a]Data from animal experiments.[b]Case study of one trauma patient.

hemorrhage is pronounced elevation of heart rate that represents a compensatory attempt to maintain adequate DO_2 in the face of a hypovolemia-induced accumulating O_2 deficit. Indeed, inadequate systemic DO_2 is viewed as the primary factor that ultimately leads to development of O_2 deficit that limits $\dot{V}O_2$max in most healthy exercising humans.[5–8,24] as well as the onset of shock for bleeding patients.[1,13,14]

Similar to exercise, the cardiac response to hemorrhage relies on optimizing cardiac output in an effort to maintain perfusion (arterial blood) pressure. Despite vast differences in cardiac filling, severe hemorrhage can elicit tachycardia greater than 120–180 beats per minute (bpm) in shock[1,32,49] similar to the pronounced elevation in heart rate of 140–200 bpm during exercise requiring maximal effort.[33,34] Whether supporting the low cardiac filling states of acute hemorrhage or high cardiac filling during physical exercise, increased cardiac rate represents a common compensatory mechanism for optimizing cardiac output.

Autonomic mechanisms. Autonomically mediated elevations in heart rate are controlled by a combination of cardiac vagal withdrawal and sympathetic nerve activation.[33] Although the direct measurement of parasympathetic nerve activity is not readily accessible in humans, the use of frequency-domain analysis R-R interval variability has provided an indirect metric for changes in cardiac vagal activity by demonstrating nearly complete elimination of the high-frequency spectra (0.15–0.40 Hz) during muscarinic receptor blockade.[50] Calculating heart rate variability (HRV) from frequency-domain analysis has revealed that significant vagal withdrawal is an underlying mechanism of increased heart rate during both hemorrhagic shock[51] and maximal exercise.[33,52,53]

Hypovolemia is a very potent stimulus for activation of sympathetic activity. Catecholamine levels in the blood have been used as an indicator for adrenergic response to hemorrhage and exercise since the relationship between HRV measures and sympathetic activity is not as established as that for cardiac vagal activity.[52] In addition to vagal withdrawal, significant elevations in heart rate can be explained by blood levels of norepinephrine (NE) that become several times normal during both physical exercise at $\dot{V}O_2$max and hemorrhagic shock (Table 1). Within minutes of the onset of hemorrhagic shock, blood levels of NE can reach as much as 10 times basal (>1800 pg/mL), enough to produce compensatory elevations in pulse rate and blood pressure.[34] Likewise, maximal heart rate responses have been associated with average elevations in plasma NE from 183 to 1337 pg/mL during graded exercise that elicited $\dot{V}O_2$max.[36]

The underlying mechanisms that elicit increased sympathetic nerve activation during physical exertion may provide insight to sympathetic control in conditions of blood loss. During exercise, heart rate can increase in the face of elevated arterial blood pressure because of a resetting of the cardiac baroreflex to a higher operating set point.[54] In contrast, the elevation in sympathetic nerve activity and heart rate associated with the central hypovolemia of hemorrhage is accompanied by reduced cardiac baroreflex sensitivity.[55] Since the pressure stimulus to arterial baroreceptors differs in direction between the hypotension associated with blood loss and the hypertension of exercise, metabolic stimuli that elicit activation of chemically-sensitive nerves in the tissues may represent a more likely common mechanism for activation of sympathetically mediated heart rate effects at $\dot{V}O_2$max and in conditions of hemorrhagic shock. There is compelling evidence that an elevated sympathetic efferent response to activation of these so-called "metaboreflexes" results in increased perfusion (arterial) pressure as a consequence of chronotropic effects on the heart, acting to increase cardiac output as well as constriction of the vasculature.[56] The end result of activating metaboreflexes in combination with baro- and chemoreflexes can result in similar magnitudes of sympathetic activation reflected by similar elevations in circulating catecholamines during hemorrhagic shock[35] and maximal exercise.[36]

Oxygen extraction ratio and tissue oxygenation. Utilizing the O_2 extraction reserve (e.g. hemoglobin bound O_2, myoglobin-bound O_2) represents a compensatory mechanism from which O_2 can be provided to cells during hemorrhage and physical exercise when DO_2 cannot meet the cellular requirement of $\dot{V}O_2$. This lowering of the O_2 extraction reserve inherently represents an O_2 deficit. In this context, measurements of the oxygen extraction ratio (OER) and tissue oxygen saturation (S_tO_2) can provide insights into the dynamics of O_2 deficit as a compensatory mechanism during intense exercise or severe hemorrhage.

OER represents the ratio of $\dot{V}O_2$ to DO_2 as the fraction of oxygen delivered to the microcirculation that is taken up by the tissues ($OER = \dot{V}O_2/DO_2$ – Figure 1).[57] Despite differences between hemorrhage and exercise in $\dot{V}O_2$ magnitude and direction, both conditions require increased OER as a contributing compensatory mechanism for maintenance of adequate $\dot{V}O_2$ in the face of inadequate DO_2. This was best demonstrated by Weiskopf *et al.*[24] when they found that the failure to reduce $\dot{V}O_2$ or elevate blood lactate in healthy humans who underwent >65% reductions in O_2–carrying capacity with whole blood withdrawal. The Weiskopf observation actually supports the contention that the only way that $\dot{V}O_2$ and lactate could remain constant in the face of reduced DO_2 was to incur an O_2 deficit by borrowing from the O_2 extraction reserve.[22] The insight to be gained from exercise is that significant O_2 deficit can be incurred without inducing significant injury in the form of organ damage or failure. In this context, O_2 deficit is indeed an adaptive and protective response as part of the compensatory reserve measurement.

The premise that DO_2crit occurs well after the onset and accumulation of O_2 deficit is a fundamental relationship that evolved from the early work in exercise physiology that demonstrated an immediate development of an O_2 deficit because of the difference between energy requirement and $\dot{V}O_2$ at the onset of exercise. It is the O_2 kinetics data obtained from physical exercise that provides the evidence

that an O_2 deficit is defined by the immediate reduction in O_2 extraction reserve. Given that fact, the data in Figure 4 clearly demonstrate that, like exercise, O_2 deficit resulting from a "borrowing" of oxygen from the O_2 extraction reserve is increased immediately upon the onset of absolute central hypovolemia (e.g. hemorrhage) in the form of reduced StO_2 with concurrent reduction in DO_2.[25] As such, the early increase in O_2 deficit represents the compensatory part of hemorrhagic shock defined as Class I and II shock by the American College of Surgeons[58] well before the onset of decompensatory Class III shock (i.e. DO_2crit).

The reliance on elevations in OER is reflected by normal resting levels of 20% to 30%[57] rising to as high as >50% during blood loss[25] and > 85–90% at $\dot{V}O_2$max.[23,33] The increase in OER estimated for hemorrhagic shock is most likely underestimated since it does not represent any reported measurements made near the point of death when OER would be maximal (far left in Figure 3). Low mixed venous oxygen saturation ($SvO_2 = DO_2 - \dot{V}O_2$) has been proposed to identify anaerobic glycolysis and global tissue hypoxia.[41] As a result of increased OER, SvO_2 is precipitously reduced from its normal resting value of 65–75%[59] to less than 20% to 30% in both hemorrhage[37] and exercise.[38]

S_tO_2 represents the amount (%) of myoglobin-bound O_2. The myoglobin disassociation curve requires a significant reduction in the partial pressure of oxygen (pO_2) in the tissue before O_2 will be disassociated from myoglobin. Indeed, tissue pO_2 has been reported to be as low as ~5 mmHg compared to a baseline level of ~34 mmHg in both hemorrhage[30] and maximal exercise.[31] A reduction in S_tO_2 reflects a compensatory increase in the availability of O_2 to support cellular $\dot{V}O_2$ in the presence of inadequate DO_2. This was best illustrated in humans undergoing progressive central hypovolemia without changing systemic $\dot{V}O_2$ or blood lactate despite significant reductions in DO_2 because of mobilization of myoglobin-bound O_2 (i.e. decreased S_tO_2) and hemoglobin-bound O_2 (Figure 4).[25] This compensatory mechanism for increasing cellular O_2 availability is reflected by a dramatic reduction in S_tO_2 from normal resting levels of ~70% to as low as ~30% during progressive central hypovolemia similar to blood loss[10] and at $\dot{V}O_2$max.[29]

Glycolysis and lactate. When $\dot{V}O_2$ can no longer meet the cellular energy demand alone, the cell becomes more reliant on energy sources of phosphocreatine and glycolysis to meet its ATP demand. Consequently, increased levels of blood lactate in the absence of adequate clearance are common to both hemorrhage and intense physical exercise. Although blood lactate is commonly measured by clinicians as a metric of shock, study of the physiology of $\dot{V}O_2$max has revealed that glycolysis and lactate production *per se* rarely accumulate because of inadequate DO_2.[4] The benign presence of blood lactate is best reflected by the observation that a high risk of shock and death is associated with elevated arterial blood lactate levels of only > 4 mmol/L during hemorrhage,[41] while blood lactate levels have been reported to be >15–25 mmol at $\dot{V}O_2$max.[40] The mechanism underlying the physiological tolerance to higher levels of blood lactate accumulation during muscle contraction compared to hemorrhage is reflected by the use of lactate as an oxidizable fuel during intense exercise, i.e. increased lactate clearance.[4,22] As such, the dynamics of lactate metabolism during intense exercise challenges the paradigm that measures of systemic blood lactate fail to provide an accurate assessment of cellular O_2 deficit in a patient with severe hemorrhage. During the absolute hypovolemia of hemorrhage, blood flow is redirected away from tissues with high mass but low energy demand (e.g. skeletal muscle) to support DO_2 to critical organs like the brain, heart, gut, liver, and kidney. Significant levels of lactate can accumulate in the brain during hemorrhage and diffuse into the blood.[60] However, the dilution of highly concentrated blood lactate leaving the brain in blood from other less metabolically-active tissues will lead to underestimation of brain lactate as an accurate measure of hemorrhagic shock. Thus, local measures of blood lactate in blood leaving specific tissues may prove to provide a more accurate clinical measure of hemorrhagic shock. Ultimately, it is not the amount of accumulated systemic blood lactate that reflects the limitation of tolerance to severe blood loss or intense exercise, but rather emergence of intolerable O_2 deficit that results from inadequate DO_2.

Acid–base buffering. In contrast to lactate, the ultimate challenge during hemorrhagic shock and $\dot{V}O_2$max is impaired removal of accumulated H^+ created by a complex number of metabolic byproducts[61] in the cells and blood that are associated with increased acidity (reduced pH). It is tissue acidity that may define the common critical factor emerging from inadequate DO_2 that leads to intolerable disturbance of cellular metabolic function. The deleterious effect of reduced cellular pH may be best reflected by the similarity in maximal arterialized blood pH of ≤ 7.0 that has been reported during bot hemorrhagic shock[32] and exercise at $\dot{V}O_2$max[39,40,61] despite a large discrepancy in accumulated blood lactate. Thus, the ability to sustain acid-base balance during progressive blood loss or intense physical exercise depends on the capacity to buffer accumulated H^+.

Another sensitive means of assessing tissue oxygenation and O_2 deficit is by measuring the base deficit, which represents the number of millimoles of base required to correct the pH of one liter of whole blood to 7.4.[41,49] Indeed, the capacity to buffer blood acidity is reflected by a high correlation between increased base deficit and reduced arterialized blood pH,[32] with base deficits > 5 mmol/L being associated with both hemorrhagic shock[32,42] and $\dot{V}O_2$max.[39]

Relatively small base deficits of only 6 to 10 mmol/L observed during hemorrhagic shock have been associated with "metabolic decompensation" when there is increasing requirements for blood transfusion[42] and the probability of death rises exponentially.[12] Although the reliance on tissue oxygen extraction reserves, phosphocreatine, and glycolysis exists with inadequate DO_2 during both hemorrhage and $\dot{V}O_2$max, it is important to recognize that intense

physical activity can result in metabolic acidosis with base deficits three to five times higher than those associated with hemorrhagic shock. This disparity of higher base deficits created by exercise is an indication that extreme changes in the acid-base balance seem to be well tolerated in healthy exercising subjects[39] compared to patients with severe blood loss. These comparisons reaffirm the notion that high levels of blood lactate are not by themselves detrimental as long as cellular metabolism is high enough to oxidize the lactate as a source of energy.[4] Thus, it is the reduction in $\dot{V}O_2$ as a consequence of lowered DO_2 during severe hemorrhage that leads to inadequate blood lactate clearance after reaching DO_{2crit} that can result in circulatory shock in the presence of relatively low blood lactate levels.

Mechanisms of pulmonary ventilation. Pulmonary ventilation is usually associated with gas exchange and is critical to the maintenance of adequate DO_2 by maintaining optimal hemoglobin saturation of the blood in both hemorrhagic shock and exercise at $\dot{V}O_2max$. However, pulmonary ventilation function also contributes significantly to acid–base balance and hemodynamics necessary for enhancing DO_2 and attenuating the accumulation of O_2 deficit at the cellular level.

Comparisons of pulmonary ventilation responses during hemorrhagic shock and $\dot{V}O_2max$ are presented in Table 1. Respiration rate (breaths per minute) increases from a resting level ranging from 10 to 20 to more than 35–40 in conditions of hemorrhagic shock[1] and $\dot{V}O_2max$.[43] This hyperventilatory response acts to create a respiratory alkalosis by removing carbon dioxide (CO_2) from the blood as a way to buffer the accumulation of H^+ and reduction in pH.[61] The respiratory alkalosis is reflected by concomitant reductions in end-tidal CO_2 below a threshold of 35 mmHg in both individuals in hemorrhagic shock[46] and exercising at $\dot{V}O_2max$.[47]

Like respiration rate, the time kinetics of the tidal volume (V_T) response to progressively increasing intensity of exercise leading to $\dot{V}O_2max$[44,45] is similar to that reported during progressive reductions in central blood volume associated with hemorrhage and leading to decompensation.[44] In both physiological conditions, V_T remains relatively unchanged until a level >80% of tolerance is reached, at which time there is an exponential increase in V_T characterized by deeper inspirations. Inspiration lowers intrathoracic pressure.[62] The greater vacuum created in the thorax by this "respiratory pump" increases venous return, cardiac filling, and cardiac output[62] which in turn may prove instrumental in sustaining systemic DO_2 through elevations in perfusion pressure during conditions of hypovolemia[10] represented by both blood loss and $\dot{V}O_2max$. Perhaps it is no surprise that patients with severe conditions of hypovolemia who gasp (i.e. the so-called "last gasp") to increase V_T have better mortality outcomes than those who do not.[48]

Compensatory reserve. The physiological parameters listed in Table 1 represent responses of compensation to the combination of accumulated tissue O_2 shortfall and inadequate DO_2 associated with hypovolemic states of hemorrhage or exercise at maximal intensity. The capacity for compensation that "protects" against low tissue perfusion during states of compromised DO_2 is known as the compensatory reserve.[10,63–65] A historical challenge has been to develop a capability to measure the integration of compensatory mechanisms, particularly as it relates to DO_2, rather than their physiological outcomes (e.g. blood pressure, SpO_2, blood pH). Novel monitoring technologies have been developed that include the application of advanced real-time signal analysis and machine learning of hundreds of thousands of photoplethysmographic waveforms during progressive states of central hypovolemia. Application of such advanced computer processing algorithms has demonstrated that measures of arterial waveform features reflect the integration of all compensatory mechanisms recruited to sustain adequate DO_2 during conditions of progressive hypovolemia with greater specificity and sensitivity compared to standard vital signs and metabolic markers.[66–70] Specifically, changing features of the ejection wave reflect the sum of all compensatory mechanisms that control myocardial function, while reflected wave features reflect the sum of all mechanisms associated with compensation for compromised cellular energy requirements.[63]

From the initial onset of hemorrhage or exercise (illustrated in Figure 3, broken lines), recruitment of the entirety of all compensatory mechanisms (e.g. autonomically-mediated tachycardia and blood flow redistribution, O_2 extraction reserve, respiration, etc.) is required to maintain adequate DO_2. With progression along the DO_2 time continuum (Figure 3), the reserve capacity to compensate would be expected to gradually deplete until energy requirements for oxygen at the cellular level can no longer be sustained during progressively severe hypovolemia. This concept is supported by a linear relationship between compensatory reserve and DO_2 (Figure 5). Ultimately, it is the depletion of compensatory reserve that leads to an inability to sustain energy requirements of the cells in the face of inadequate DO_2 that leads to

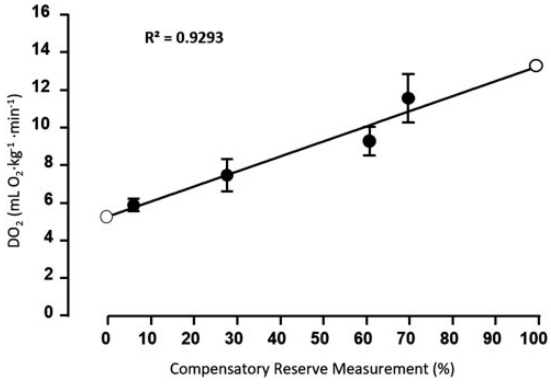

Figure 5. Linear regression of the relationship between systemic oxygen delivery (DO_2) and compensatory reserve measurement (CRM) expressed by DO_2 (mL $O_2 \cdot kg^{-1} \cdot min^{-1}$) = 0.08 × CRM (%) + 5.3. Open circles represent extension of the regression line to 0% and 100% CRM. Data, collected from non-human primates, are expressed as mean ± SEM; N = 12. Modified from Koons *et al*.[71]

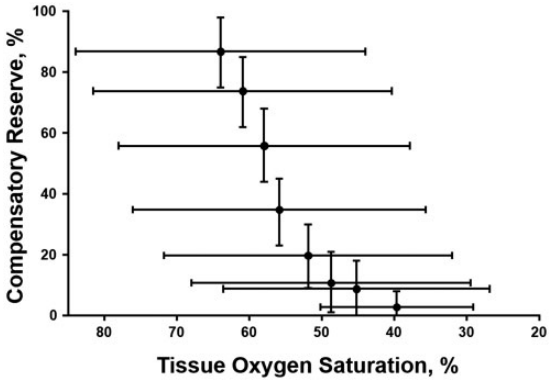

Figure 6. Relationship between tissue oxygen saturation and compensatory reserve. Symbols are average (±95% CI) values generated from 55 healthy volunteer subjects exposed to 0, −15, −30, −45, −60, −70, −80 and −90 mmHg LBNP. Amalgamated $r^2 = 0.965$. Modified from Convertino and Sawka.[10]

impending hemodynamic decompensation from blood loss[63,72] or failure to continue muscular work at $\dot{V}O_2$max.[10]

Individual variability in compensatory responses: A different perspective. Although the physiological responses listed in Table 1 represent generalizable direction and magnitude of changes in both conditions of hemorrhagic shock and physical work at $\dot{V}O_2$max, it is recognized that there exists significant individual variability in tolerance to tissue deoxygenation and O_2 deficit. This variability is most apparent from the data presented in Figure 6 that illustrates large differences in tissue oxygen saturation across levels of hypovolemia, making it impossible to distinguish some individuals with >85% of compensatory reserve from some individuals with <5% reserve to compensate. The data presented in Figure 6 also indicates that there remains >30% of tissue oxygen saturation in most individuals who have very little remaining capacity to compensate. Consistent with these data, actual measured $\dot{V}O_2$max has been reported to be only ~90% of the theoretical $\dot{V}O_2$max calculated from mitochondrial oxidative capacity with significant individual variability.[73] Taken together, these observations support the notion suggested by others[4] that tissue oxygen *per se* is not necessarily a primary limiting factor in development of intolerable O_2 deficit.

One approach to test this hypothesis is to compare individual variability in global compensatory response to hypovolemia in normal sedentary people to exercise-trained individuals and world class endurance athletes who have extraordinarily high blood volume, capillary density, cellular mitochondrial content, and aerobic enzyme activities.[19,23] If tissue capacity for storing and utilizing oxygen contributes to mitigating the accumulation of O_2 deficit, it might be expected that the endurance athlete's physiology designed to support high $\dot{V}O_2$max would be reflected by high tolerance to absolute central hypovolemia such as severe hemorrhage. Contrary to this notion, there is consistently reported observations in the literature that individuals who participate in endurance exercise activities (e.g. marathon runners) demonstrate some degree of physiological compromise to their blood pressure regulation leading to a higher incidence of symptomatic syncope in conditions of central hypovolemia compared to non-athletes.[74–76] This observation is reasonable when consideration is given to the evidence that endurance-trained athletes demonstrate a steeper slope of the Frank–Starling relation that translates to greater reductions in stroke volume for equal falls in left ventricular filling volume.[75] Consequently, the steep Frank–Starling curve that provides endurance athletes a great physiological advantage during competitive running can predispose them to decompensation in the face of severe central hypovolemia such as during hemorrhage by compromising DO_2. The comparison of physiological functions in endurance athletes, sedentary individuals, and chronic heart failure patients support the notion that, in the end, the limiting factor to reaching hemorrhagic shock or $\dot{V}O_2$max is inadequate DO_2 to meet the need to maintain cellular O_2 demand.[4,73] Thus, it is not enough to measure either tissue oxygen or DO_2, but individual variability demands measurements that reflect both factors to assure a most accurate assessment of which combination of compensatory mechanisms dictates either hemorrhagic shock or $\dot{V}O_2$max in each individual. It is for this reason that measurements of arterial waveform features provide the most accurate assessment of either hemorrhagic shock or $\dot{V}O_2$max since features of the ejected wave represent the sum total of all mechanisms that dictate systemic DO_2, while features of the reflected wave represent the impact of metabolism that influences cellular $\dot{V}O_2$ and accumulated tissue O_2 deficit.[63]

Hemorrhagic shock vs. $\dot{V}O_2$max conceptual framework: Other factors to consider

In addition to sharing key common physiological features, it is important to consider that reaching the threshold of hemorrhagic shock or $\dot{V}O_2$max will depend on the rate of accumulated O_2 deficit during blood loss or maximal oxygen uptake. For instance, a patient suffering from a slow venous bleed may sustain a progressively increasing acidotic state for an extended period of time without succumbing to hemorrhage. This slow hemorrhage condition would be physiologically equivalent to a healthy individual who performs a prolonged period of submaximal exercise above the threshold for blood lactate accumulation. On the other hand, an injury to a major artery that results in rapid exsanguination and imminent death would be analogous to a sprint exercise that reaches $\dot{V}O_2$max in a short time period, both conditions resulting in rapid imbalance between oxygen demand and oxygen supply that cannot be resolved because of a limitation to DO_2. The physiology of hemorrhagic shock is also complicated by the notion that individual tissues (e.g. gut, brain, muscle) during blood loss varies in their tolerance to low DO_2, which may be analogous to the varying patterns of tissue oxygen demands during physical exercise that are defined by the inverse relationship between power and speed duration.

Clinical translation from the exercise experience

Accurate guidance for resuscitation of patients suffering from hemorrhagic shock represents a significant challenge to emergency medicine caregivers in their efforts to avoid the sequela associated with over- or under-resuscitation. A metric of inadequate DO_2 reflects the most sensitive quantifier of the degree of shock,[13] but accurate assessment of DO_2 has been limited by technology gaps in the ability to measure a bleeding trauma patient's O_2 shortfall and repayment O_2 extraction reserve in real time.[13] As a result of this monitoring limitation, use of devices in pre-hospital critical care medicine that provide measures of blood lactate or tissue oxygen saturation has been proposed.[13,77] However, challenges associated with the use of blood lactate or tissue oxygen as surrogate measures of compromised DO_2 for guidance to clinical intervention are numerous. First, blood lactate levels do not necessarily reflect pathophysiology since their rise at $\dot{V}O_2$max in young healthy individuals is multiple times that observed with hemorrhagic shock (Table 1) without clinical consequence. Second, DO_2 during hemorrhage can be decreased during the early stages of compensatory shock in the absence of elevated blood lactate. Third, although tissue oxygen is reduced during hemorrhage and at $\dot{V}O_2$max, there remains adequate cellular O_2 levels indicated by ~30% to 50% of resting baseline (Table 1). As such, clinical and exercise evidence indicates that it is likely that measures of blood lactate or tissue oxygen saturation may misrepresent the DO_2 status of a patient with hemorrhagic shock.

The key to effective resuscitation in patients with hemorrhagic shock is an appreciation "that it is not enough to simply halt the accumulation of oxygen debt (i.e. shortfall); it (O_2 shortfall) must be repaid."[13] The challenge, however, is that the clinical community has not realized a way to assess O_2 shortfall in real time.[13] Figure 5 provides data obtained from experiments conducted on healthy baboons illustrating that measurement of the capacity to compensate (i.e. compensatory reserve) during whole blood resuscitation is closely correlated to DO_2.[71] These results reflect the ability of changing features of the arterial waveform to provide a real-time measurement of integrated mechanisms that contribute to control of physiological factors that influence the development of O_2 deficit. As such, it is compensatory reserve data collected with measures of exercise O_2 deficit during exercise that provide a basis for using such technology for early identification of bleeding patients with hemorrhagic shock and for guiding accurate fluid or whole blood resuscitation leading to O_2 deficit repayment.

Summary

Evidence provided by a cross-sectional review of the literature supports our conceptual framework that hemorrhagic shock in bleeding patients and $\dot{V}O_2$max of endurance athletes shares similar physiological responses initiated by a requirement to avoid critical levels of accumulated tissue O_2 deficit in response to inadequate DO_2 associated with states of hypovolemia (Figure 1). In both physiological conditions, hypovolemia initiates a similar complex cascade of compensatory responses that include (but are not limited to) vagally- and sympathetically-mediated tachycardia, increased oxygen extraction from the blood and tissue O_2 extraction reserves, and hyperventilation acting to optimize acid–base balance and central hemodynamics. With a finite capacity to maintain adequate DO_2, the sum total of all compensatory responses eventually can be depleted without repayment of the O_2 deficit. With this progression of events, and individual variability, a critical threshold of DO_2 is reached, requiring a marked increase in the energy contribution from glycolysis to supplement the energy required by the tissues for normal function that can no longer be provided by aerobic metabolism alone. The resulting impairment in removal of accumulated H^+ leads to a reduction in pH (cellular acidity) that, if not reversed, will lead to a disturbance of normal cell metabolic function as reflected by irreversible shock in the case of hemorrhage or physical exhaustion when $\dot{V}O_2$max is reached.

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