Cardiogenic Shock: Failure of Oxygen Delivery and Oxygen Utilization

Hoong Sern Lim, MD, FRCP, FESC

Department of Cardiology, University Hospital Birmingham NHS Trust, Birmingham, United Kingdom

Address for correspondence:
Hoong Sern Lim, MD, FRCP, FESC
University Hospital Birmingham NHS
Foundation Trust
Edgbaston, Birmingham, B15 2TH
United Kingdom
sern.lim@uhb.nhs.uk

ABSTRACT

Cardiogenic shock remains a highly lethal condition. Conventional therapy including revascularization and mechanical circulatory support aims to improve cardiac output and oxygen delivery, but increasing basic and clinical observations indicate wider circulatory and cellular abnormalities, particularly at the advanced stages of shock. Progressive cardiogenic shock is associated with microcirculatory and cellular abnormalities. Cardiogenic shock is initially characterized by a failure to maintain global oxygen delivery; however, progressive cardiogenic shock is associated with the release of pro-inflammatory cytokines, derangement of the regulation of regional blood flow, microcirculatory abnormalities, and cellular dysoxia. These abnormalities are analogous to septic shock and may not be reversed by increase in oxygen delivery, even to supranormal levels. Earlier mechanical circulatory support in cardiogenic shock may limit the development of microcirculatory and cellular abnormalities.

Introduction

Low cardiac output despite adequate or elevated filling pressure is one of the defining features of cardiogenic shock. As cardiac output is a key determinant of global oxygen delivery (DO_2), cardiogenic shock can also be defined as a failure of global DO_2 to meet oxygen consumption (VO_2), resulting in tissue hypoperfusion. The mortality rate from cardiogenic shock in acute myocardial infarction (AMI) remains stubbornly high despite revascularization[1] and hemodynamic support.[2] This review will discuss the concept of DO_2, the wider circulatory and cellular changes, and the therapeutic implications in cardiogenic shock.

Global Oxygen Delivery

Global DO_2 is the total oxygen carried (convected) by blood to tissue and is calculated as the product of the oxygen content in arterial blood (CaO_2) and the cardiac output (CO). Oxygen in blood is usually estimated from hemoglobin (Hb) concentration (Hb in g/L), the amount of Hb that has oxygen bound to it (percent saturation), and the partial pressure of oxygen (PO_2) dissolved in plasma (Figure 1):

$$O_2\text{content} = (k_1 \times \text{Hb} \, x \, \%\text{saturation}) + (k_2 \times PO_2)$$

This is expressed as milliliters of oxygen per liter of blood, where k_1 is the Hüfner constant and k_2 is

the solubility coefficient of oxygen, which is 0.003 mL of oxygen dissolved/mm Hg/dL of plasma. Dissolved oxygen contributes little to total oxygen content due to the limited solubility. Hence, DO_2 is a function of Hb concentration, oxygenation, and CO:

$$DO_2 = CO \times (1.36 \times \text{Hb} \, x \, \%\text{saturation}) + (0.003 \times PO_2)$$

Oxygen Delivery in Response to Oxygen Consumption

Oxygen delivery is responsive to (patho-)physiological changes in any of the 3 components of DO_2 (Hb, oxygenation, and CO) and changes in VO_2. In the case of acute hypoxia or acute anemia, CO increases to maintain normal DO_2. However, there is no acute compensatory mechanism for acute reduction in CO. Acute reduction in DO_2 due to a drop in CO (eg, AMI) when VO_2 is unchanged is "compensated" by greater oxygen extraction (ER), resulting in a drop in mixed venous oxygen saturation (SvO_2; Figure 2).

Oxygen delivery is also responsive to the changing metabolic needs and VO_2, exemplified by the increase in DO_2 when VO_2 increases from rest to exercise (mediated almost completely by an increase of CO). The proportionate increase in DO_2 maintains the ratio of delivery to consumption (DO_2-VO_2 ratio) at approximately 5:1. This DO_2-VO_2 ratio is high enough that cellular respiration is not supply-dependent, and VO_2 is predominantly a function of tissue oxygen demand: "consumption drives delivery." Failure to maintain the DO_2-VO_2 ratio is initially compensated by increased oxygen extraction and fall in mixed venous oxygen content. Studies have suggested
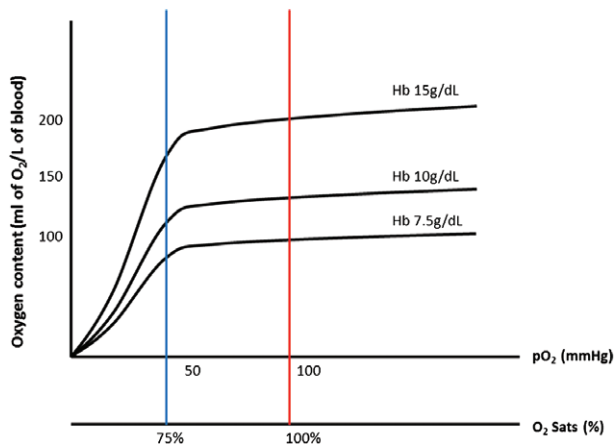
Figure 1. Oxygen content as a function of hemoglobin concentration and oxygenation. Abbreviations: Hb, hemoglobin; PO_2, partial pressure of oxygen; sats, saturations.
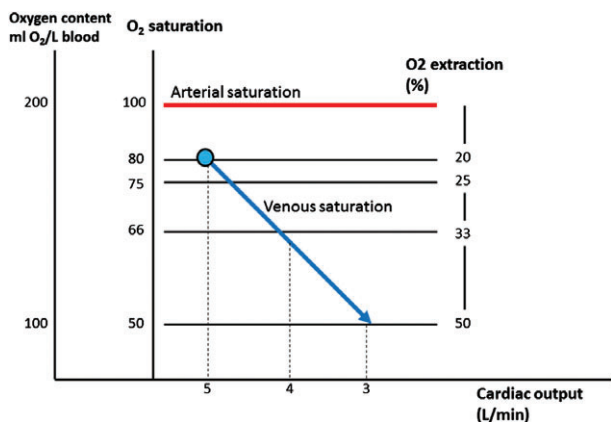

Figure 2. Increase in oxygen extraction with reduction in mixed venous saturation with reduction in cardiac output.

Figure 3. Oxygen consumption becomes supply (DO_2)-dependent when the DO_2-VO_2 ratio falls below 2:1. The blue dashed line indicates higher critical DO_2 threshold (eg, in splanchnic circulation) and apparent supply-dependent increase in VO_2 as oxygen debt is repaid. Abbreviations: DO_2, oxygen delivery; VO_2, oxygen consumption.

VO_2 becomes supply-dependent when the DO_2-VO_2 ratio falls below 2:1, producing a biphasic DO_2-VO_2 relationship (Figure 3).[3] This critical level of DO_2-VO_2 relationship—so-called critical DO_2—corresponds to the maximal oxygen extraction.

Below this critical level of DO_2, VO_2 falls in a near-linear fashion with ensuing tissue hypoxia. The cells become almost completely reliant on inefficient anaerobic metabolism, generating adenosine triphosphate (ATP) at relatively low rates, and at the unsustainable cost of acidosis induced by unopposed ATP hydrolysis and lactic acid accumulation. "Oxygen debt" occurs because of the excessive production of lactic acid, which, in the absence of oxygen, is a metabolic end product. Restoration of DO_2 before irreversible tissue death repays this oxygen debt, resulting in transient increase in VO_2 as DO_2 is increased (producing an apparent supply-dependent increase in oxygen uptake), lactic acidosis is cleared, and organ dysfunction is reversed.[4] Therefore, intuitively, correction of DO_2 should improve survival from cardiogenic shock.
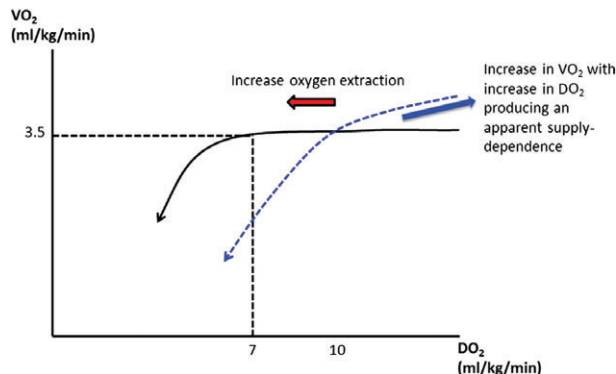
Beyond Global Oxygen Delivery in Cardiogenic Shock

Mortality in cardiogenic shock has often been attributed to the downward spiral associated with progressive pump failure and loss of CO and DO_2. As such, the management of cardiogenic shock has centered on the correction and optimization of CO and DO_2. However, although reduction in CO and DO_2 are defining hemodynamic features of cardiogenic shock, a significant proportion of patients perish despite improvement and even normalized CO and DO_2. In addition, many of these patients have succumbed to a state of low systemic vascular resistance analogous to septic shock, despite improvement in DO_2.[5] The latter suggests wider circulatory and cellular abnormalities with progression of cardiogenic shock.

Regional Blood Flow and Oxygen Consumption

Under normal physiological conditions, metabolic demand alters local arteriolar tone to direct the necessary increase in regional blood flow to the appropriate tissues: "demand drives supply." The arteriolar smooth muscles actively contract in response to a range of systemic autonomic nervous, humoral, and local mediators, through a number of receptor types that are distributed with great organ-to-organ variability. Arteriolar smooth-muscle relaxation is mediated principally by the synthesis and release of nitric oxide (NO) by the vascular endothelium, which, via soluble guanylate cyclase and generation of cyclic adenosine monophosphate, effects the inhibition of cross-bridge cycling in the smooth muscle and relaxation.[6] The arteriolar smooth-muscle activity in critical organs with high metabolic activity may be subjected to additional controls, based on oxygen availability within the organ.

Many of the (auto-)regulatory mechanisms may be lost with the development of the systemic inflammatory response syndrome (SIRS), due to inflammatory mediator–induced abnormalities of the NO system. The increased expression of inducible nitric oxide synthase (iNOS) and excess NO production induces vasodilation. The variable expression of iNOS in different organs and

different vascular beds within an organ results in heterogeneous flow with abnormally high blood flow and pathological shunting in some vascular beds with high iNOS activity (if coupled with impaired oxygen utilization) with diminished response to catecholamines, and underperfusion of areas lacking iNOS. The abnormal distribution of blood flow and shunting of blood extends into the microcirculation due to endothelial damage/dysfunction and allows leukocyte adhesion and formation of microthrombi. The consequent "consumption-perfusion mismatch" and "shunting" of blood across metabolically nonactive (or relatively less active) tissues may result in regional tissue hypoxia despite normal (or even supranormal) DO_2. Hence, SvO_2 may be normal/elevated in the presence of regional tissue hypoxia, and measures of global DO_2 may not reflect local tissue oxygen levels during critical illness and SIRS. Indeed, hypoxia in specific organs is often the result of disordered regional distribution of blood flow both between and within the organs, and not due to inadequacy of global DO_2-VO_2 matching.

Cardiogenic shock may be complicated by the development of SIRS,[7] particularly with increased duration of shock (in the absence of infection).[8] The level of pro-inflammatory cytokine interleukin-6 is elevated in cardiogenic shock and may achieve levels comparable with septic shock.[9] The excessive NO production results in vasodilation that contributes to the adverse hemodynamics in cardiogenic shock, as evidenced by the increase in blood pressure with NG-monomethyl-L-arginine in patients with persistent shock despite vasopressors.[10] This increase in blood pressure with NG-monomethyl-L-arginine was not associated with reduction mortality in a randomized trial,[11] possibly due to the nonspecific inhibition of NO production or adverse effects on ventriculoarterial coupling in patients with severe cardiac dysfunction.[12]

This regional difference or mismatch in blood flow is compounded by regional variation in the threshold of critical oxygen delivery, with the development of SIRS.[13,14] In the critically ill patient, some parts of the body may become ischemic at higher levels of DO_2, such as the gut mucosa.[15] The reduction in splanchnic perfusion by endogenous and the use of exogenous vasoconstrictors, coupled with an increase in the critical DO_2 threshold with SIRS,[16] reduces the tolerance for reduced DO_2 and increases the susceptibility to splanchnic ischemia. The failure to maintain enteral nutrition also compromises the integrity of the gut mucosa. Splanchnic ischemia and loss of gut mucosal integrity allow translocation of endotoxin and bacteria into the portal circulation, overwhelming hepatic clearance and exacerbating widespread endothelial damage and inflammatory response. Treatment aimed at maintaining or improving splanchnic perfusion may reduce the incidence of multiple organ failure and mortality,[17] although this has not been examined specifically in patients with cardiogenic shock.

Microcirculatory Blood Flow

The regional regulation of blood flow extends to the microcirculation, including capillaries where oxygen diffusion to the tissues takes place. Hemorheology and capillary patency are the main determinants of capillary blood flow. Hemoglobin in the red blood cell may function as an oxygen sensor during hypoxia, enabling the red blood cells to regulate blood flow by releasing the vasodilators NO and ATP.[18] The vascular endothelium, by modulating local coagulation/fibrinolysis and leukocyte migration through the release of biologically active factors such as NO, prostacyclin, adenosine, and endothelin, influences microcirculatory blood flow.[19] Endothelial damage and exposure to the subendothelium facilitate leukocyte and platelet aggregation that results in microthrombosis and local tissue hypoxia.

Of note, it is red blood cell flow specifically, and not blood in general, that determines oxygen delivery, because oxygen has a low solubility in plasma. Red blood cells facilitated by the oxygen-carrying capacity of Hb are largely responsible for the convective transport of oxygen by the blood. In the microcirculation, capillary hemodynamics can be quantified as red blood cell flux (expressed as red blood cells per second), also termed red blood cell supply rate.[20] Red blood cell flux accounts for both red blood cell velocity (V, in mm/s) and capillary hematocrit or red blood cell lineal density (LD, as red blood cell/mm):

$$\text{Red blood cell flux} = V \times LD$$

Oxygen flow in capillaries (qO_2) can then be calculated from the red blood cell flux, the red blood cell saturation, and the oxygen-carrying capacity of a single red blood cell ($K = 0.0362$ mL oxygen/red blood cell at 100% oxygen saturation),[21] analogous to the global oxygen delivery equation:

$$qO_2 = \text{red blood cell flux} \times \text{oxygen saturation} \times K$$

Also analogous to the global DO_2 parameters, capillary oxygen extraction ratio (ERc) can be calculated from difference in capillary oxygen flow rates at the arterial, or inflow into the capillary (qO_2in) and venous, or capillary outflow (qO_2out):

$$ERc = (qO_2in) - (qO_2out) / (qO_2in)$$

The alteration in microvascular geometry, capillary hemodynamics, functional capillary density, and microvascular oxygen transport in SIRS produces microvascular blood flow heterogeneity and consequent oxygen flow heterogeneity. Capillary oxygen extraction will be greater in microvascular beds with lower qO_2, with ensuing hypoxia when the ERc is exhausted, which may contribute to tissue/organ injury and failure in critically ill patients.

A number of studies have documented microvascular abnormalities in patients with cardiogenic shock. First, forearm blood flow using venous plethysmography at rest and reactive hyperemia were diminished in a subgroup of patients with cardiogenic shock, indicating increased vasoconstriction and an impaired capacity for vasodilation.[22] Second, the proportion of perfused small vessels ($<20\,\mu m$) and perfused capillary density were lower in patients with cardiogenic shock,[23] and the lower proportion of perfused vessels was associated with poorer survival. Third, diminished sublingual perfused capillary density at baseline or following treatment was associated with development
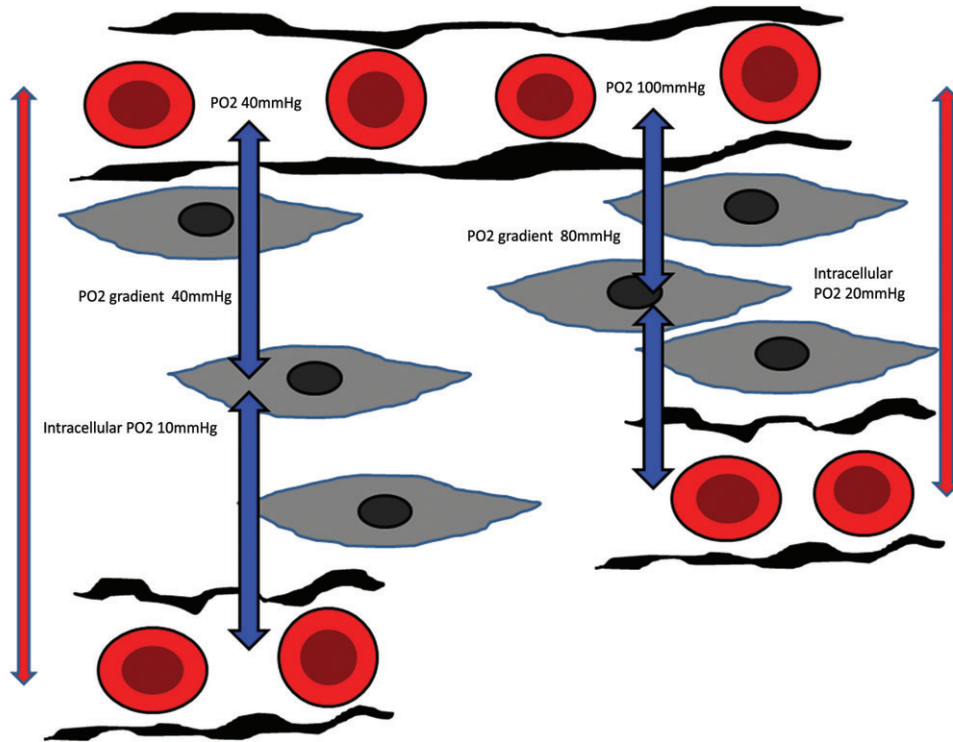
Figure 4. Oxygen diffusion in the microcirculation. Blue vertical arrows indicate the oxygen diffusion distance. Typical diffusion distances may range from 10 to hundreds of microns. Red vertical arrows indicate intercapillary distance. Abbreviations: PO_2, partial pressure of oxygen.

of multiorgan failure and poor outcomes in patients with AMI complicated by cardiogenic shock.[24] Improvement in microcirculatory abnormalities in patients with acute heart failure has been described with low-dose nitroglycerin,[25] but this has yet to be validated in clinical trials. It is not clear if these microcirculatory abnormalities can be limited by earlier correction of DO_2.

Microcirculatory Oxygen Diffusion

Oxygen diffuses over relatively short distances from arterioles and capillaries in all directions based on the local PO_2 gradient. Oxygen diffusion is limited by oxygen solubility (k), oxygen diffusivity (D), and the PO_2 gradient (dPO_2/dr). The PO_2 gradient drives the net movement of oxygen from a region of high PO_2 to a region of low PO_2. Oxygen flux can be described by Fick's first law of diffusion:

$$\text{Oxygen flux} = -kD \times dPO_2/dr \text{ (the negative sign}$$

$$\text{rectifies the negative slope of the gradient)}$$

The oxygen diffusion distance is the distance from the Hb in red blood cells to the mitochondria (Figure 4). The critical oxygen diffusion distance, which is the maximum distance that mitochondria can be away from an oxygen source without impaired function, is determined by these oxygen diffusion parameters and by capillary PO_2 and tissue oxygen consumption. The intercapillary distance may be increased under hypoxic conditions, particularly "hypoxic" hypoxia (low arterial PO_2) and tissue edema (increased vascular permeability or excessive fluid administration;

Figure 4). Hence, in the microcirculation, it may be PO_2 rather than DO_2 (ie, diffusion rather than convection) that is vital for local tissue oxygenation. Avoiding tissue edema by avoiding excessive fluid loading and early treatment of congestion and arterial hypoxemia may improve tissue/cellular oxygenation.

Cellular Oxygen Utilization

Eukaryotic cells are generally dependent on aerobic metabolism, as mitochondrial respiration offers greater efficiency for extraction of energy from glucose than anaerobic glycolysis. Molecular oxygen readily diffuses from Hb in the capillary into the cell and the mitochondrion. In the mitochondria, molecular oxygen is the terminal electron acceptor in the electron transport chain, which is a series of protein complexes, residing in or near the inner mitochondrial membrane. The flow of electrons down this chain results in conformational changes in the protein complexes and the translocation of protons from the mitochondrial matrix to the inter membrane space. The resultant difference in both charge and proton concentration in the 2 compartments is the proton motive force that converts an intermittent supply of fuel into a constant supply of ATP.[26]

Inadequate perfusion from limitation in DO_2 and consequent hypoxia has long been the prevailing pathophysiological model behind multiorgan dysfunction syndrome (MODS).[27] Indeed, optimization of DO_2 in the early period of shock when the cellular energetic machinery is still functional may ameliorate the impending cellular energetic
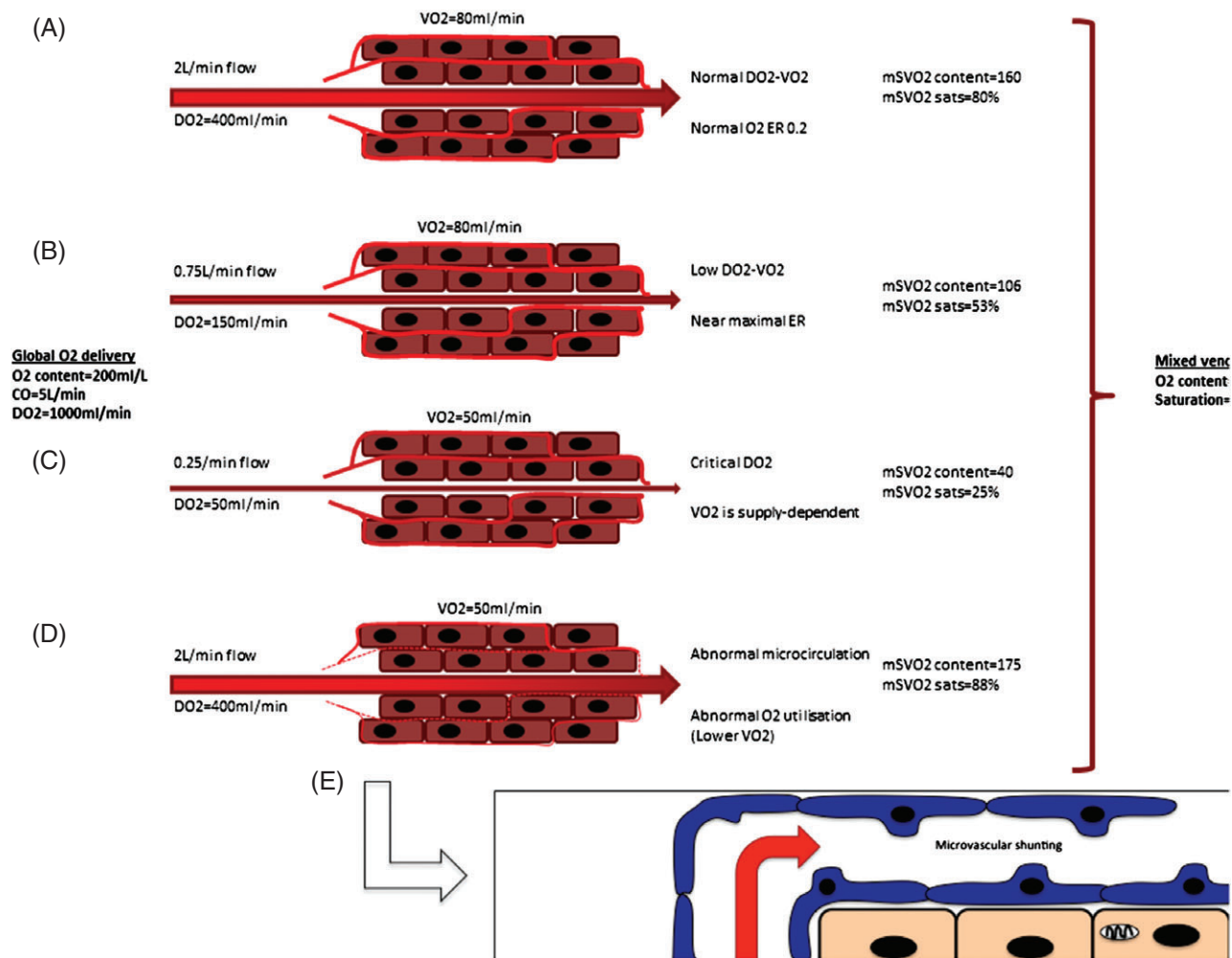
Figure 5. Global oxygen delivery is distributed variably to a number of vascular beds. (A) A normal oxygen delivery-consumption (DO_2-VO_2) relationship results in normal ER and normal $mSVO_2$. (B) Reduction in blood flow (eg, vasoconstriction) reduces the DO_2-VO_2 relationship, which is compensated by increased ER and reduced $mSVO_2$. (C) Oxygen consumption becomes supply-dependent when blood flow and DO_2 drop below the critical oxygen delivery threshold. (D, E) Cellular oxygen uptake is poor even with normal blood flow in the presence of microcirculatory abnormalities and cellular cytopathic dysoxia, resulting in high $mSVO_2$. The overall $mSVO_2$ may remain normal despite regions of critical hypoxia. Abbreviations: CO, cardiac output; DO_2, oxygen delivery; ER, oxygen extraction ratio; $mSVO_2$, mixed venous oxygen saturation; VO_2, oxygen consumption.

failure and reduce the incidence/severity of organ dysfunction. However, progression of the shocked state is characterized by the failure to utilize oxygen to produce ATP due to mitochondrial failure, resulting in cytopathic hypoxia. The cells, in the face of inadequate energy due to mitochondrial dysfunction, decrease metabolic activity, which manifests clinically as multiorgan dysfunction (including sepsis-related cardiomyopathy).[28] In this regard, organ dysfunction may be an adaptive response to severe inflammatory response. Hence, impaired DO_2 and the development of SIRS may instigate mitochondrial dysfunction. The latter, and not DO_2, becomes the dominant pathophysiology in MODS,[29] with the corollary that a strategy of increasing DO_2 (even to supranormal levels) will be of little benefit.

Mitochondrial dysfunction has not been well studied in patients with cardiogenic shock. However, the evolution of the dominant pathophysiological processes corresponds well with clinical observation that shock responds better to hemodynamic resuscitation in the early stages[30] and suggests that avoiding cellular dysoxia may limit the development of the syndrome of multiorgan dysfunction. The efficacy of specific intervention targeting cellular dysoxia and mitochondrial dysfunction is also likely to be dependent on the evolving pathophysiology.

Therapeutic Implications

The progression of cardiogenic shock is accompanied by the development of SIRS, vasodilation, regional circulatory abnormalities, microcirculatory abnormalities, and cellular dysoxia, a clinical phenotype that resembles septic shock (Figure 5). At these latter stages, efforts to improve blood flow to regionally hypoxic tissues by increasing DO_2 (even to supranormal levels) are inefficient and even harmful.[31] In addition, studies on the treatment of septic shock with the so-called goal-directed therapy, which is predicated on the optimization of DO_2, produced little/no significant benefit[32]

(see Supporting Information, Table, in the online version of this article), despite encouraging results in earlier studies,[33] further highlighting the limitations of medical manipulation of DO_2 in the advanced stages of shock.

This pathophysiological evolution of cardiogenic shock has clinical implications:

1. Inotropes are routinely used to improve CO in cardiogenic shock, but at the expense of tachyarrhythmias, increased myocardial VO_2, and adverse effects on regional blood flow.[34] It is possible that earlier and effective mechanical circulatory support to improve DO_2, while avoiding the potential toxicity associated with high-dose catecholamines, may improve outcomes in cardiogenic shock. Acute mechanical circulatory support, including percutaneous microaxial pumps and extracorporeal life support (venoarterial membrane oxygenation), or surgical cannulation of the heart with extracorporeal ventricular assist devices, increases total blood flow and DO_2[35] and has been successfully used to bridge patients with cardiogenic shock to recovery, transplantation, or an implantable left ventricular assist device.[36]

2. Impaired DO_2 and tissue hypoxia is a well-described (anaerobic) cause of high lactate levels. However, microcirculatory abnormalities may also result in anaerobic elevation in lactate levels, independent of global hemodynamic changes.[37] In addition, lactate levels may be elevated in the absence of impaired global DO_2 from epinephrine use or failure of pyruvate metabolism due to mitochondrial dysfunction. Therefore, lactate levels become unreliable for tissue hypoxia in critically ill patients with SIRS.[38] Persistently elevated lactate may indicate microcirculatory abnormalities or cytopathic hypoxia, which may not be corrected (and even may be exacerbated) by escalation of vasopressors or inotropes and is associated with poor outcomes.[39]

3. Central or mixed venous blood oxygen saturations are widely used to guide treatment of critically ill patients. However, mixed venous blood represents the final admixture of venous blood from multiple vascular beds and may conceal regional changes in blood flow, microcirculatory abnormalities, or cytopathic hypoxia (Figure 5). Measurements of SvO_2 complement blood lactate levels in guiding the management of critically ill patients; concomitant measurement of both may be more useful than the exclusive use of one or the other.

4. Therapeutic interventions aimed at the microcirculation and manipulation of cellular oxygen utilization (eg, the regulated induction of a hypometabolic state resembling hibernation may help the energy-starved cell, whereas the stimulation of mitochondrial activity during the latter phases of shock may improve recovery)[28] may be of benefit in advanced stages of shock.

Conclusion

Cardiogenic shock is characterized by a global reduction in DO_2 due to reduction in CO, but the pathophysiology evolves with progression of shock into a hemodynamic phenotype more analogous to septic shock. Early and effective restoration of DO_2 and limiting the toxicity associated with inotropes and catecholamines with mechanical circulatory support to abrogate this evolution of the shock phenotype deserves further study. Regional DO_2 may be improved by exploiting the differences in receptor population and density between different vascular beds to redirect blood flow from relatively overperfused tissues to underperfused "vital" organs. Pharmacological treatment aimed at the microcirculation and manipulation of cellular oxygen utilization may also prove fruitful in the treatment of advanced cardiogenic shock.

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