Pharmacological Optimization of Tissue Perfusion

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Abstract

Inadequate perfusion if prolonged, leads to irreversible cellular injury and multiple organ failure and eventually, death. Therefore early identification of perfusion deficit in its reversible state is important to improve outcome of treatment and reduce associated morbidity and mortality. The most important aspect in monitoring the critically ill patient is the detection of life-threatening derangements of vital functions.

Key word

* *Tissue Perfusion*

* *Optimization*

* Cardiovascular monitoring
* Inadequate tissue perfusion

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ABG	Arterial Blood Gases
APACHE II	Acute Physiology and Chronic Health Evaluation II
ARDS	Acute Respiratory Distress Syndrome
ASA	American Society of Anesthesiology
ATLS	Advanced Trauma Life Support
CaO_2	Arterial Oxygen Content
CCO	Continuous Cardiac Output
CI	Cardiac index
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CVP	Central Venous Pressure
DIC	Disseminated Intravascular Coagulopathy
Do_2	Oxygen Delivery
DPAP	Diastolic Pulmonary Artery Pressure
DPG	2,3-Diphosphoglycerate
ECG	Electrocardiogram
FFP	Fresh Frozen Plasma
H_2O	Water
HBOCs	Hemoglobin-Based Oxygen Carriers
HES	Hydroxyl Ethyl Starch
HS	Hemodynamic Shock
HTS	Hypertonic Saline
HTS-D	Hypertonic Saline with Dextran
ICU	Intensive Care Unit
I/R Injury	Ischema/Reperfusion Injury
LR	Lactated Ringer's Solution
LVEDP	Left Ventricular End-Diastolic Pressure
LVEDV	Left Ventricular End-Diastolic Volume
MAP	Mean Arterial Pressure
MODS	Multiple Organ Dysfunction Syndrome
MPAP	Mean Pulmonary Artery Pressure
MTPs	Massive Transfusion Protocols
NaCl	Sodium Chloride
O_2	Oxygen
OEC	Oxygen Equilibrium Curve
OER	Oxygen Extraction Ratio
PAC	Pulmonary Artery Catheter
$PaCO_2$	Arterial Partial Pressure of Carbon Dioxide
PaO_2	Arterial Partial Pressure of Oxygen
PAOP	Pulmonary Artery Occlusion Pressure
PAWP	Pulmonary Artery Wedge Pressure

PDD	Pulse Dye Densitometry
PEEP	Positive End Expiratory Pressure
$PiCO_2$	Gastric Intramucosal PCO_2
pRBCs	Packed Red Blood Cells
PVR	Pulmonary Vascular Resistance
SBP	Systolic Blood Pressure
SIRS	Systemic Inflamatory Response Syndrome
SPAP	Systolic Pulmonary Artery Pressure
SvO_2	Mixed Venous Oxygen Saturation
$ScvO_2$	Central Venous Oxygen Saturation
SVR	Systemic Vascular Resistance
TEE	Trans Esophageal Echocardiography
TEPs	Trauma Exsanguination Protocols
TTE	Trans Thoracic Echocardiography
VASST	Vasopressin in Septic Shock Trial
Vo_2	Oxygen Consumption

Optimizing tissue perfusion does not simply mean improving arterial pressure, cardiac output, or both, but rather delivering oxygen from the lungs to the mitochondria in amounts adequate to sustain required metabolism.[1]

An adequate supply of oxygen and substrate to mitochondria that enables sufficient oxidative ATP production to match metabolic demands can be considered the absolute priority of the circulation. Consideration of the three components of the oxygen delivery equation (cardiac output, hemoglobin concentration, and arterial oxyhemoglobin saturation) allows the clinician to formulate an appropriate management response in the face of a specific cardiorespiratory problem. However, tissue oxygen delivery is a global measure and does not necessarily reflect changes occurring within an organ bed, nor whether the amount delivered is adequate for metabolic needs. [2]

Vital signs are the first available clinical indicators of well-being in the ward or emergency department. Low arterial pressure, tachycardia, impaired mental status, chest pain, delayed capillary refill, and/or decreased urinary output, should trigger an urgent attempt to diagnose and correct the impaired circulation.[3] Hemodynamic bedside monitoring by pulmonary artery catheters (PAC) has been considered by many as the “gold standard” for critically ill patients,[4] but its usefulness has been challenged recently, leading to emergence of multiple less invasive hemodynamic monitoring systems that provide similar information to that of the PAC. Other indicators of tissue perfusion include tissue oxygenation monitoring and new technologies as laser Doppler flowmetry, [5] near infrared spectroscopy[6] and others.

The initial management using fluid resuscitation and vasoactive drug treatment represent the major cornerstone for correcting any major impairment of the circulation which strongly impairs organ perfusion.[7] However, debate still rages as to the choice of agent, dose, timing, targets, and monitoring modalities that should optimally be used to benefit the patient yet, at the same time, minimize harm.[8]

This study aims to highlight importance and factors affecting tissue perfusion, novel techniques used for measuring tissue perfusion, as well as general shock syndrome management including fluid resuscitation and vasoactive treatments for inadequate tissue perfusion, and the specific treatment of the triggering causes.[9] As much as selecting the ‘best’ agent to use, it is also necessary to discuss how best use can be obtained from these drugs, recognizing they carry a multitude of often concealed side-effects.

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1. Physiology of Tissue Perfusion

Physiology of Tissue Perfusion

An adequate supply of oxygen and substrate to mitochondria that enables sufficient oxidative ATP production to match metabolic demands is considered the absolute priority of the circulation.[2] Consideration of the three components of the oxygen delivery equation (cardiac output, hemoglobin concentration, and arterial oxyhemoglobin saturation) allows the appropriate management response in the face of a specific cardiorespiratory problem. However, tissue oxygen delivery is a global measure and does not necessarily reflect changes occurring within an organ bed, nor whether the amount delivered is adequate for metabolic needs.

At the organ level, blood flow and perfusion pressure are controlled by extrinsic factors, including neurological (e.g. sympathetic innervation), biochemical (pH, $P\text{co}_2$, and $P\text{o}_2$), hormonal (renin–angiotensin system), and vasoactive mediators (e.g. nitric oxide and prostaglandins). Autoregulation represents intrinsic control, whereby afferent arteriolar tone changes as a result of modifications in perfusion pressure. However, organs do not behave in the same fashion regarding flow dependency. The kidney, brain, and myocardium are considered to autoregulate themselves (i.e. their regional blood flow is held constant within an arterial pressure range). Consequently, below and above these thresholds, organs may encounter ischemia or a luxury perfusion that could potentially increase edema formation and jeopardize perfusion.[2]

Microcirculation and its Role in Regulation of Tissue Perfusion:

The microcirculation is taken to include vessels<150 μm in diameter. It therefore includes arterioles, capillaries, and venules. Another definition based on arterial vessel physiology rather than diameter is proposed, depending on the response of the isolated vessel to increased internal pressure. By this definition, all those arterial vessels that respond to increasing pressure by a myogenic reduction in lumen diameter are included in the microcirculation, as well as the capillaries and venules. [10]

Functions of microcirculation:

1. In addition to providing the large surface area needed for blood-tissue exchange, a primary function of the microcirculation is to optimize nutrient, oxygen supply within the tissue in response to varying metabolic requirements.
2. An important function is to avoid large fluctuations in hydrostatic pressure at the level of the capillaries causing disturbances in capillary exchange. The pre-capillary elements of the microcirculation protect the fragile capillaries from the potentially damaging pressures that occur in the larger arteries.[11]
3. It is at the level of the microcirculation that a substantial proportion of the drop in hydrostatic pressure occurs. Large and medium sized arteries and veins offer relatively little resistance to the flow of blood, and some 70% to 90% of the systemic arterial pressure is delivered to the microcirculation, where the main resistance to flow is offered.[12] It therefore, largely determines local and overall peripheral resistance, and it is also the site where the earliest manifestations of cardiovascular disease (the inflammatory processes) occur. [13]

Importance of Hemorheological Factors for Tissue Perfusion:

Proper tissue metabolism and function are highly dependent on adequate blood supply, and most tissues are well equipped with vascular control mechanisms that keep the blood supply and the metabolic demand of the tissue in balance. Vascular flow resistance is a function of geometric factors, often termed “vascular hindrance” and viscosity related factors. Although the vascular flow (rheology) has been recognized and studied for many decades, the importance of the blood rheological properties as has only recently been appreciated. It showed that impairments of mechanical properties of RBCs and

WBCs, should result in impaired tissue perfusion. However, the relative importance of hemorheological factors in pathophysiological processes is still unclear because of the following:

1. The interactions between blood rheological factors and hemodynamics are highly complex. Thus, for normal tissue in which the vasculature has sufficient regulatory ability, rheological alterations may be compensated for by an appropriate change of vascular geometry. However, if the vasculature is disturbed by disease processes (e.g., arteriosclerosis), vascular regulatory mechanisms may not be sufficient to compensate for changes of blood rheology.[14]

2. Blood rheological factors (e.g., plasma viscosity, RBC deformability, RBC aggregation, WBC activation) are sensitive to the metabolic status of the tissue being perfused. Any changes within the tissue, such as ischemia or infection, could readily affect the rheological properties of the various cellular elements in blood and thus alter one or more aspects of its behavior. Thus there often is difficulty in determining cause and effect relations in pathophysiological states.

Acute disease pathology can compromise normal physiological responses so conventional concepts such as autoregulation may not necessarily apply. For example, age and chronic diseases such as hypertension are also associated with circulatory remodeling and blood composition changes. Septic shock is associated with increased spatial and temporal microcirculatory heterogeneity, whereas perfusion thresholds may be blunted. As a consequence, little is known about the best perfusion pressure to target in an individual patient, particularly one who is critically ill.[14]

2. Oxygen Delivery

Factors Affecting Oxygen Delivery

All cells require oxygen for aerobic metabolism to maintain normal cellular function. Because oxygen cannot be stored in the cells, a constant supply that precisely matches the metabolic needs of each cell is required. Failure to deliver sufficient oxygen to the tissues even for a few minutes may develop tissue hypoxemia resulting in anaerobic metabolism and production of lactate which if prolonged, may result in organ dysfunction, as seen in many forms of under resuscitated shock.[15]

Oxygen Transport:

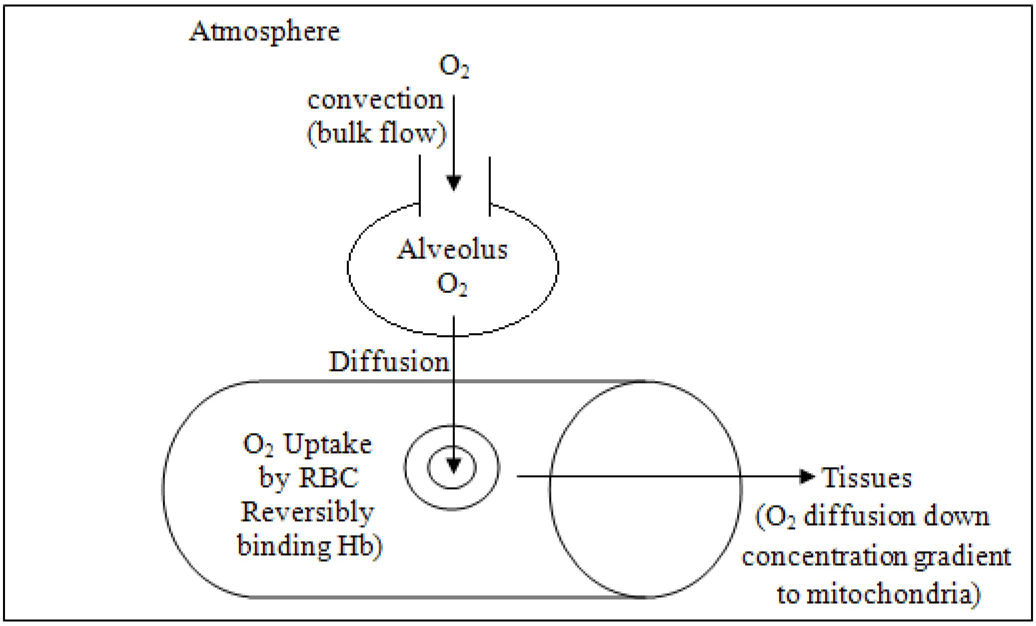

Figure (1): Oxygen transport from atmosphere to tissues. [15]

Fick's Law is relevant in describing Do_2 (oxygen delivery):

$$O_2 \text{ diffusion} = K \text{ x } S/\tau \text{ x } \Delta P$$

where diffusion of oxygen from the alveolar air into the blood or from the blood into the tissue is described by the Fick law, which states that diffusion of oxygen is directly proportional to the permeability of oxygen within the diffusion medium (K), surface area for diffusion (S), and pressure gradient (ΔP)