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Systematic Review

Current data regarding homeostasis of tissues oxygenation in pathophysiological and therapeutic circumstances

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Abstract: Oxygen is essential for cellular respiration and energy production. Tissue oxygenation refers to delivering oxygen to cells throughout the body. Microcirculation brings blood through small sanguine vessels to maintain the cells' supply of nutrients and oxygen. Optimal tissue oxygenation and microcirculation are essential for maintaining healthy tissue. Conversely, poor oxygenation can cause tissue damage, impair wound healing, and increase infection risk. Several factors can affect tissue oxygenation and microcirculation, including age, lifestyle factors (such as smoking and stress), and underlying medical conditions (such as diabetes and high blood pressure). To improve tissue oxygenation and microcirculation, individuals can engage in healthy lifestyle habits such as regular exercise, healthy eating, stress management, and avoiding smoking. Tissue oxygenation can also be looked therapeutic, given that topical and cosmetic treatments such as massage, pelotherapy, hydrotherapy, moisturizers, and certain skin care products can help promote healthy microcirculation at the somatic level. In the scientific literature, the focus is on hypoxia rather than tissue oxygenation. This article proposes a paradigm shift and emphasizes the homeostatic importance of microcirculation and tissue oxygenation in pathophysiological and therapeutic circumstances. The systematic review of the data from the last 2 years (2021-2022) and the meta-analysis performed on tissue oxygenation will contribute to the practical approach to the pathology circumscribed to tissue oxygenation.

Keywords: Tissue oxygenation; Hypoxia; Microcirculation; Homeostasis; Microenvironment

1. Introduction

Throughout a lifetime, humans consume nearly 12 million liters of O_2 (1). The homeostasis of tissue oxygenation and blood microcirculation is critical in maintaining health (2). Under pathophysiological conditions, tissue oxygenation can be compromised due to

poor perfusion, inadequate oxygen delivery, or defective oxygen utilization, leading to tissue hypoxia, subsequently generating cell damage, inflammation, and even cell death (3). Therapeutic interventions to improve essential homeostatic parameters include oxygen therapy (4), hyperbaric oxygen therapy (5,6), physical therapy(7), hydrotherapy (8), or pelotherapy (9).

Inflammation can affect tissue oxygenation in various ways. First, inflammation can cause vasodilation or constriction of blood vessels, affecting blood flow and oxygen delivery to the tissues. Second, inflammatory cells can produce reactive oxygen species (ROS) that can damage cells and reduce tissue oxygenation (10). Third, inflammation can lead to edema or the accumulation of fluid in the tissues, which can compress blood vessels and reduce blood flow and oxygen delivery (11). Chronic inflammation can lead to tissue fibrosis and further impair tissue oxygenation. (12).

Proper tissue oxygenation is critical for maintaining cellular homeostasis and preventing apoptosis. Inadequate oxygenation, or hypoxia, can induce apoptosis through various mechanisms, including activating pro-apoptotic signaling pathways and generating reactive oxygen species (ROS) (13). Hypoxia can increase the expression of anti-apoptotic proteins, which may contribute to cancer progression and treatment resistance, but on the other hand, excessive oxygenation, or hyperoxia, can also induce apoptosis, primarily through the generation of ROS. Therefore, achieving optimal tissue oxygenation levels prevents apoptosis and promotes cellular health (14).

The oxygen transport cascade begins with the intake of atmospheric oxygen through the lungs, where it diffuses through the alveolar membrane and enters the bloodstream (15). The oxygen is then bound to the hemoglobin molecules in the red blood cells and transported through the circulatory system to the tissues. Although it takes only about 2 μs for an oxygen molecule to diffuse across the 0.1 μm distance, 0.5 ms is required to transport O_2 over 1 μm. O_2 could diffuse a distance of 1 cm in almost 15 hours (1). Considering Fick's laws for diffusion (1), the organism must combine the sequences of convective and diffusive transport by designing a circulatory system composed of macro- and microcirculatory segments (16). The efficiency of the oxygen transport cascade is influenced by several factors, including atmospheric oxygen concentration, the diffusing capacity of the lungs and tissues, the availability of hemoglobin and other oxygen-binding molecules, and the metabolic demands of the tissue (1).

From more than 500 liters of oxygen utilized daily by tissue cells of a normal human subject, mitochondria are essential for cellular energy production, as they use over 90% of molecular oxygen consumed by cells. However, incomplete reduction in aerobic metabolism can result in reactive oxygen species (ROS) formation (17). As a result, a small fraction of oxygen consumed by the respiratory chain is incompletely reduced. Furthermore, if not efficiently removed, ROS accumulation can produce hydroxyl radicals through the Fenton reaction in the presence of Fe^{2+} or Cu^{+}, which can cause oxidative damage to cellular components, including nucleic acids, proteins, and lipids (18).

The human body requires high aerobic respiration to function properly (19). Under aerobic conditions, pyruvate is converted to acetyl coenzyme A (acetyl CoA) in the presence of the enzyme pyruvate dehydrogenase. Acetyl CoA enters the Krebs cycle leading to the formation of several cofactors, which, through oxidative phosphorylation, generate 36 ATP molecules. Under anaerobic conditions, pyruvate is transformed into lactic acid under the action of lactate dehydrogenase, regenerating NADH and allowing glycolysis and ATP generation. Lactic acid is dissociated into hydrogen ions and lactate in an aqueous solution and at physiological pH. Numerous studies have shown the relationship between tissue hypoxia and lactate production (20), with a sudden increase in lactate concentration when oxygen consumption becomes limited by low oxygen intake (4).

Regulation of tissue oxygenation is crucial for an organism's survival and proper functioning. Coordination between the respiratory and cardiovascular systems, blood flow regulation, and erythropoietin production is essential for maintaining tissue oxygenation. At the body's level, tissue oxygenation regulation is primarily determined by the

balance between oxygen demand and supply. The body responds to changes in oxygen supply, such as changes in altitude or blood loss, by adjusting the delivery of oxygen to the tissues. This is done by regulating cardiac output, blood flow distribution, and blood's ability to carry oxygen. The body can also increase oxygen extraction from the blood by increasing capillary density and improving mitochondrial tissue function (15). Blood flow is carefully regulated in tissues with high metabolic demand, such as actively contracting muscles to ensure oxygen supply matches the request.

At the cellular level, the regulation of tissue oxygenation involves the cell's oxygen-sensing mechanisms, such as hypoxia-inducible factors (HIFs) (17). Myogenic regulation relies on the smooth muscle cells' inherent properties in the arterioles' walls. These cell signaling pathways respond to changes in oxygen levels (21) by regulating gene expression to promote hypoxia adaptation, angiogenesis, and glycolysis (22). In addition, various molecular carriers, such as hemoglobin and myoglobin, facilitate the transport and storage of oxygen within cells. Humoral and tissue vasoactive agents include bradykinin, angiotensin II, vasopressin, natriuretic peptides, free catecholamines, and many others, all acting through receptor-operated channels of vascular smooth muscle cells VSMCs and endothelial cells. Local metabolic effects, particularly effective in terminal arterioles, are primarily caused by changes in pO2, pCO2, osmolarity, pH, potassium ion concentration, and released catabolites such as adenosine. Numerous vasoactive substances cause the generation of the vasodilatory autacoids NO and prostaglandin I2 (PGI2) via endothelial receptors found on endothelial cells in most sections of the vascular tree, but primarily those of terminal arterioles. In contrast to endothelium-mediated vasodilator actions, most agonists cause vasoconstriction when they gain direct access to abluminal VSMC because the corresponding receptors on smooth muscle cells activate calcium influx and IP3-diacylglycerol pathways (1). The endothelium is not only a passive membrane or a barrier between blood and tissues.

On the contrary, it is also actively involved in many functions, such as controlling and regulating vascular tone, exchanging fluids and dissolved substances, hemostasis and coagulation, and inflammatory responses. The permeability of the endothelium to small solutes is highly dependent on the presence and number of endothelial fenestrae, and thus the structure of the fenestrae-bound glycocalyx is interesting. In addition, the endothelial surface plays a significant role in regulating coagulation and fibrinolysis (23). Therefore, endothelial glycocalyx damage should directly increase microvascular hydraulic conductance and enhance permeability to all plasma constituents. Such damage occurs in hypoxia, inflammation, postischemic reperfusion, volume expansion, and mechanical manipulation of the heart, to name the most common causes (4). PROSPERO ID: 413680.

2. Methods and tools

In this article, we have used an elaborated and dedicated protocol about the current data regarding homeostasis of tissues oxygenation in pathophysiological and therapeutic circumstances, with the following main steps:

1. Search strategy: Our systematic literature review regarding tissue oxygenation included searching related articles published between January 1, 2020, and March 31, 2023, indexed in reputable international medical databases: National Center for Biotechnology Information (NCBI)/PubMed, NCBI/PubMed Central (PMC), Elsevier, Nature, Wiley, and Institute for Scientific Information (ISI) Web of Knowledge/Science (via ISI Thomson Reuters index check). For searching, we used the specific keywords syntax: "tissue oxygenation". In the total pool of articles, by brainstorming in the authorship group, we then oriented the selection to dedicated subsections of our article, like oxygen monitoring or different pathologies identified in the narrative introduction, or to correlate scientific data with therapeutic data applications. Table 1 shows the numerical results of our search, which was based on a focused, step-by-step classification according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (24) regarding scientific articles identification and selection (see Figure 1).

2. A new algorithm was developed to evaluate each article's scientific impact and quality. Specific instruments and tools were used to ensure qualitative support and data validation, including bias interrogation checklists: Cochrane Risk of Bias Tool: https://www.ncbi.nlm.nih.gov/books/NBK132494/bin/appf-fm1.pdf, AMSTAR Checklist: https://amstar.ca/Amstar_Checklist.php, and JBI Critical Appraisal Checklist: https://jbi.global/critical-appraisal-tools. The algorithm considers several factors, such as the year of publication, the total number of citations, and the PEDro score, which measures the quality of clinical trials. Using this algorithm, the articles were assessed and ranked according to their scientific merit and relevance to the field. In addition, the algorithm was customized to meet our evaluation's specific needs, allowing for a more objective and standardized assessment of the articles. The selected papers were inputs for a Benchmarking analysis strategy (25). The "paradigm funnel" (26) was used to obtain relevant reports regarding tissue oxygenation, being considered a research tool for emphasizing the importance of evidence-based data (27).

3. Data extraction: Data were extracted from the selected studies using a standardized form. The following information was collected: study design, sample size, population characteristics, intervention or exposure intervention, outcome measures, and results. In addition to these data, it is essential to consider the various physio-pathological and therapeutic circumstances that can influence tissue oxygenation. For example, tissue hypoxia can occur due to decreased oxygen delivery or increased oxygen demand in conditions such as sepsis, shock, or acute respiratory distress syndrome (ARDS). Therapeutic interventions such as mechanical ventilation, vasopressor support, or blood transfusion may be used to restore tissue oxygenation in these cases. In contrast, in conditions such as chronic obstructive pulmonary disease (COPD), tissue hypoxia can result from impaired oxygen diffusion due to lung damage. In these cases, oxygen therapy, pulmonary rehabilitation, or bronchodilator therapy may improve tissue oxygenation. Therefore, understanding the physio-pathological and therapeutic circumstances influencing tissue oxygenation is critical for developing effective interventions to improve tissue oxygenation and overall health outcomes.

4. Data synthesis and analysis: A narrative synthesis was conducted to summarize the findings of the selected studies. The studies were organized based on their study design, population characteristics, intervention or exposure intervention, outcome measures, and results. Data were analyzed descriptively to identify common themes and patterns.

The findings of the selected studies suggest that tissue oxygenation is critical for homeostasis and proper physiological function. Furthermore, dysregulation of tissue oxygenation can lead to various pathological conditions, such as hypoxia and ischemia. These conditions can result from multiple factors, including injury, disease, and environmental stressors.

5. Graphical techniques and tools, such as data collection sheets, graphic representations, critical examination matrices, cause-effect diagrams, Pareto charts, control sheets, and correlation diagrams, were used to analyze, interpret and present the obtained data and to elaborate our systematic review article.

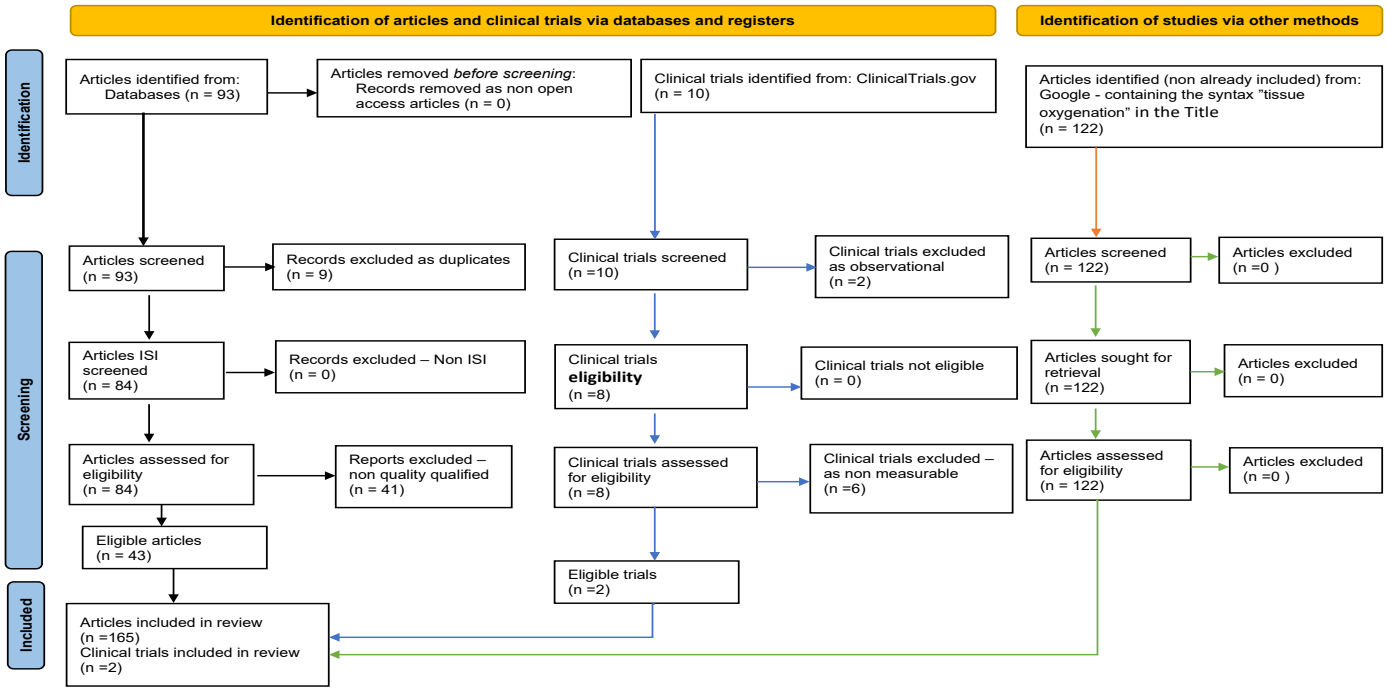

Figure 1. Adapted PRISMA flow diagram, customized for our study.

Table 1. Keywords sets-based search for related articles—numerical results in specific international scientific databases.

Keywords	Elsevier	PubMed	Nature	Wiley	Web of Science	Total
"tissue oxygenation"	8	9	12	6	58	93
Articles after duplicates exclusion						84
Articles after non-relevant exclusion						43

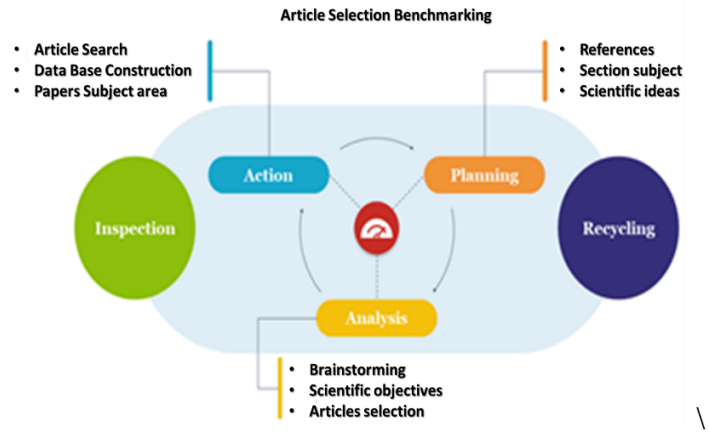

Figure 2. Article selection method and analysis, customized for our study, adapted after the Benchmarking strategy.

3. Monitoring of microcirculation and tissue oxygenation level

Monitoring microcirculation and tissue oxygenation level has become increasingly important in clinical practice to assess the adequacy of tissue perfusion and oxygenation and can help guide resuscitation efforts in critically ill and optimize patient outcomes. Methods of monitoring microcirculation and tissue oxygenation include:

1. Capnography - Measures the level of carbon dioxide in the blood to assess tissue oxygenation indirectly (28).

2. Pulse oximetry is a noninvasive method that measures arterial hemoglobin oxygen saturation and allows the measurement of central venous oxygen saturation. Phenomena such as systemic microvascular shunting can falsify the result (29). Pulse oximetry displays HbO2 saturation for a hemodynamic event in the macrocirculation, not the microcirculation (30). The main disadvantage of pulse oximetry technology is its limitation in monitoring HbO2 saturation during oxygen therapy, including patients' exposure to hyperoxic conditions. Oxyhemoglobin saturation is measured by illuminating tissue at two wavelengths: 585 nm and 577 nm. At 585 nm, the absorption properties of oxyhemoglobin and deoxyhemoglobin are the same, so changes in tissue blood volume are reflected in emitted light. At 577 nm, oxyhemoglobin has higher absorbance than deoxyhemoglobin, so light intensity is affected by oxygenation levels and blood volume changes. Subtracting 585 nm reflectance changes from those at 577 nm provides a parameter that correlates with net changes in blood oxygenation. (12).

3. Near-infrared spectroscopy (NIRS) - a noninvasive tool for assessing tissue oxygen saturation (StO2) and, indirectly, microcirculatory function (4), recording the absorption of infrared light by oxygenated and deoxygenated hemoglobin (31). According to the Beer-Lambert laws, the attenuation of light by a chromophore is proportional to its absorption coefficient and optical path length (32). NIRS allows for real-time monitoring of muscle oxygenation (33).

4. Laser Doppler - Measures blood flow by analyzing the frequency of laser light reflected by moving red blood cells. Lightguide tissue spectrophotometry is a new approach combining laser Doppler flowmetry and tissue spectrometry to evaluate skin microvascular blood flow and oxygenation (34).

5. Transcutaneous Oxygen Monitoring (TCOM) - a noninvasive method of measuring tissue oxygenation through the skin using electrodes (35). It involves using an electrode placed on the skin to measure the partial pressure of oxygen (PO2) in the underlying tissue (36). TCOM helps evaluate tissue oxygenation in patients with circulation issues, diabetes, and wound care needs. However, it has limitations due to sensitivity to temperature, pressure, and measurement errors due to moisture (31).

6. The blood oxygen level-dependent (BOLD) effect in magnetic resonance imaging (MRI) is used for the noninvasive exploration of brain functions. Recent studies have quantified the BOLD signal and combined it with MR_StO2 measurements to estimate the cerebral metabolic rate of oxygen (CMRO2). This method provides valuable information and can replace the more invasive PET imaging. (37). Pathologic conditions of skeletal muscle can also be studied (38).

7. Microcirculation can be measured directly using sensitive video microscopes, such as the third-generation portable microscope, CytoCam-IDF. This microscope uses incident dark-field illumination and automated real-time digital image analysis to visualize the microcirculation. Tissue oxygenation can be measured continuously, and dynamic measurements can be obtained after short periods of arterial occlusion. The resulting data can be used to derive desaturation, resaturation, and hyperemia slopes correlated with oxygen consumption and microvascular reactivity, providing detailed information about the microcirculatory function. (39).

8. Hyperspectral imaging monitoring is a noninvasive technique that uses light to visualize and measure changes in tissue oxygenation and microcirculation (40). This technology works by emitting light of multiple wavelengths onto tissue, which is then absorbed and scattered by tissue molecules, including hemoglobin and water. The reflected or transmitted light is then detected and analyzed to determine oxygenated, deoxygenated, and total hemoglobin levels. This monitoring system has numerous applications in clinical settings (41), including assessing tissue perfusion and oxygenation in patients with circulatory shock, sepsis, and other critical illnesses (42). It can also monitor wound healing, assess skin graft viability, and guide surgery (43).

4. Tissue oxygenation in various pathological circumstances

Several pathologies interfere with tissue oxygenation. Hypoxia can be an acute clinical symptom or consequence, leading to cell damage, impaired organ function, and organ failure if not addressed promptly (44). Clinically, tissue hypoxia (45) can manifest as symptoms such as shortness of breath, rapid heartbeat, fatigue, confusion, and cyanosis (blue tint to the skin or mucous membranes). Tissue hypoxia can also result from certain medical treatments, such as radiation therapy or chemotherapy for cancer, which can damage blood vessels and reduce blood flow to tissues. In these cases, monitoring tissue oxygenation levels and implementing interventions to improve oxygen delivery can be critical for maintaining patient health (46).

4.1. Tissue oxygenation – and dermatological pathological conditions.

Tissue oxygenation is critical in healing various conditions, such as burns, bedsores, and wounds (47). For example, in burns, tissue oxygenation is disrupted due to the destruction of blood vessels and reduced blood flow to the affected area. This lack of oxygenation can lead to tissue death and slow healing (48). Likewise, in bedsores or pressure ulcers, tissue oxygenation is reduced due to the pressure on the skin, which restricts blood flow and leads to tissue damage (49). Similarly, tissue oxygenation is crucial for healing wounds, as oxygen is essential for cellular metabolism and tissue regeneration. Factors that can affect tissue oxygenation in these conditions include patient age, underlying medical conditions, and the severity of the injury. The biochemical, physicochemical, and mechanical considerations necessary for a successful skin substitute appear to be best met by designing an artificial dermis capable of interfacing with host tissue, assuring tissue oxygenation, and controlling water loss (50) and bacterial invasion (51).

Systemic sclerosis (SSc) is characterized by autoimmunity, microangiopathy, and tissue fibrosis. Hypoxia, caused by reduced blood flow and increased extracellular matrix (ECM), is a hallmark feature of SSc and may contribute to disease progression (17). Hypoxia stimulates the production of ECM proteins and aggravates vascular disease in SSc by disrupting vascular endothelial growth factor (VEGF) receptor signaling. Furthermore, chronic VEGF over-expression due to hypoxia may result in the formation of chaotic vessels with decreased blood flow. Therefore, hypoxia is thought to play a central role in the pathogenesis of SSc by augmenting vascular disease and tissue fibrosis (17).

4.2. Cardiovascular diseases and tissue oxygenation

Atherosclerosis is a pathological condition that can significantly impact tissue oxygenation. This disease involves the accumulation of fatty deposits on the inner lining of the arterial walls, narrowing and hardening the arteries, which can reduce blood flow to vital organs and tissues. In addition to lowering blood flow, atherosclerosis can increase the risk of blood clots, further exacerbating tissue hypoxia (52).

Coronary artery disease (CAD) is a common form of heart disease that occurs when the arteries that supply blood to the heart become narrow or blocked due to plaque buildup (53). This can reduce blood flow and oxygen delivery to the heart muscle, producing tissue hypoxia (54).

Peripheral arterial disease (PAD) is a condition that affects the blood vessels outside the heart and brain, primarily in the legs. Reduced blood flow to the extremities in PAD results in tissue hypoxia, impairs wound healing and can lead to amputations. The hallmark symptom of PAD is claudication, which is leg pain or discomfort during physical activity. In severe cases, patients may experience rest pain, ulceration, or gangrene. Tissue oxygenation measurements in PAD can assess disease severity, monitor the response to treatment, and predict outcomes (55).

Impaired skin microcirculation is a major predisposing factor in inflammation and ulceration in patients with chronic venous insufficiency (56) and venous ulcers (57). Increased capillary filtration rate predisposes to the formation of edema. Blood circulation is regulated by sympathetic adrenergic vasoconstrictor nerve fibers in the acral regions of

the human body and distal limbs. Compression bandages can have effects on microcirculation (58).

4.3. Respiratory diseases and tissue oxygenation

Chronic obstructive pulmonary disease (COPD) is a lung disease that involves a complex interplay between chronic inflammation, oxidative stress, and tissue remodeling, resulting in structural changes in the lungs and a reduced ability to oxygenate the blood (59). As a result, patients with COPD commonly experience hypoxemia, or low blood oxygen levels, which can lead to tissue hypoxia and subsequent organ damage. The management of COPD involves improving oxygenation, reducing inflammation, and managing symptoms to improve the patient's quality of life (60).

Asthma is a chronic respiratory disease characterized by inflammation and narrowing of the airways, which can lead to shortness of breath, wheezing, and chest tightness. In asthma, tissue oxygenation is compromised due to the reduced availability of oxygen caused by the decreased airway diameter. Reduced oxygen supply can lead to hypoxemia, characterized by low blood oxygen levels (61). Chronic hypoxemia can lead to complications, including pulmonary hypertension, right-sided heart failure, and impaired brain function (62).

In Acute Respiratory Distress Syndrome (ARDS), a severe lung injury, there is significant damage to the alveoli in the lungs, leading to impaired gas exchange and reduced tissue oxygenation (63). This reduction in oxygen supply can cause hypoxemia, leading to various complications, including organ failure and death (64).

4.4. Hematologic diseases and tissue oxygenation

Anemia is characterized by decreased red blood cells or reduced hemoglobin in the blood. Hemoglobin is responsible for carrying oxygen from the lungs to the tissues, and a reduction in its availability can lead to tissue hypoxia. In anemia, tissue oxygenation is compromised due to the reduced capacity of the blood to carry oxygen (65). Chronic hypoxemia leads to impaired immune function, cognitive deficit, and cardiovascular disease (66).

Sickle cell disease is an inherited blood disorder characterized by abnormal hemoglobin, which can cause red blood cells to become sickle-shaped and rigid. These abnormal cells can get stuck in small blood vessels, reducing blood flow and tissue hypoxia. As a result, in sickle cell disease, tissue oxygenation is compromised. Chronic hypoxemia can lead to complications, including pulmonary hypertension, stroke, and organ damage (67).

4.5. Neurological diseases and tissue oxygenation

Stroke is a medical emergency that occurs when blood flow to the brain is interrupted due to a blood clot or a ruptured blood vessel (68). In stroke, tissue oxygenation is compromised due to the decreased blood flow to the affected area of the brain. This reduction in oxygen supply can cause tissue damage and, if left untreated, can lead to permanent brain damage or death (69). Hypoxemia can occur in severe cases, leading to various complications, including seizures, respiratory failure, and cardiac arrest (70).

Traumatic brain injury (TBI) is a condition characterized by damage to the brain caused by an external force. In TBI, tissue oxygenation is compromised due to the decreased blood flow to the affected area of the brain (71). This reduction in oxygen supply can cause tissue damage and, if left untreated, can lead to permanent brain damage or death. Trauma, tissue injury, is responsible for initiating the hypothalamic-pituitary-adrenal axis, the immunological and metabolic responses triggered to restore homeostasis. Tissue damage, hemorrhage, pain, and fear are critical components of any traumatic event. Trauma and blood loss result in cardiovascular responses, increasing heart rate, systemic vascular resistance, and maintaining blood pressure (BP) to vital organs at the expense of blood flow to the gut and skeletal muscle. Severe trauma causes exuberant

physiological, immunological, and metabolic changes that predispose to organ dysfunction, a systemic inflammatory response, infection, and multiple organ dysfunction (72).

4.6. Metabolic diseases and tissue oxygenation

In diabetes, tissue oxygenation is compromised due to the damage that high blood sugar levels can cause to blood vessels. This damage can lead to reduced blood flow and tissue hypoxia. Chronic hypoxemia can lead to various complications, including peripheral neuropathy, kidney disease, and cardiovascular disease (16). Studies show that tissue oxygen saturation is generally decreased in patients with diabetes. Blood flow in the diabetic foot tissue is redirected from the main tract channel of the metarterioles by bypassing the exchange capillaries. Thus, cells become hypoxic regardless of tissue blood flow, and arterial oxygen is not consumed, although venous oxygen saturation remains high (73). Autoregulation is particularly important in tissues like the retina, which lack an adrenergic sympathetic nerve supply (74).

Metabolic acidosis is a pathological condition characterized by decreased blood pH due to acid accumulation resulting from increased production or decreased excretion of hydrogen ions (75). Tissue oxygenation is impaired in metabolic acidosis because acidosis causes a shift of the oxyhemoglobin dissociation curve, leading to reduced oxygen uptake by the tissues. In addition, acidosis can also lead to decreased cardiac output, reducing tissue perfusion and oxygen delivery (76). Metabolic acidosis can occur in various pathological conditions, such as kidney failure, diabetic ketoacidosis, and lactic acidosis (77). The severity of metabolic acidosis is typically assessed by measuring arterial blood gas parameters, including pH, partial pressure of carbon dioxide, and bicarbonate levels (14).

Obesity has been found to harm microcirculation (78). In addition, tissue pressure, inflammation, and oxidative stress can all lead to endothelial dysfunction, characterized by impaired vasodilation and increased vascular tone. Obesity has also been found to have a negative impact on wound healing. Obesity can also impact macrocirculation, which refers to blood flow through larger vessels such as arteries and veins (79). In addition, oxygenation patterns and altered tissue oxygenation affect whole-body homeostasis (80).

4.7. Tissue oxygenation - a critical aspect of patient care in the intensive care unit (ICU).

In the ICU, tissue oxygenation is typically monitored through noninvasive or invasive techniques (81). ICU patients with respiratory failure, sepsis (82), or shock are at particular risk for tissue hypoxia and impaired oxygen delivery (83), making tissue oxygenation monitoring essential in these cases (84).

In sepsis, the microcirculation can become dysfunctional, leading to hypoperfusion and tissue hypoxia, which fires cellular dysfunction and eventually multiple organ failure (20). The heterogeneity of capillary blood flow can also contribute to the development of tissue hypoxia, as only a portion of the capillaries usually is perfused even under normal conditions (85). Abnormal microvascular perfusion, including decreased functional capillary density and increased blood flow heterogeneity, is observed during the initial phases of the body's systemic inflammatory reaction to infection and appears to have prognostic significance in sepsis. (39). In early hemorrhagic shock, reactive arterio-constriction will reduce precapillary hydrostatic pressure, thereby reducing fluid filtration into the interstitial space (1).

Disturbances in microcirculatory homeostasis have been implicated in the pathophysiology of multiple organ dysfunction syndrome. The underlying mechanisms involve complex interactions between various factors such as increased heterogeneity of capillary blood flow, reduced deformability of erythrocytes, endothelial cell dysfunction with increased permeability and apoptosis, alteration of vasomotor tone, increased number of activated neutrophils with more neutrophil-endothelial interactions, and activation of the coagulation cascade with the formation of microthrombi. In addition, Vasomotion, which is the oscillation of vascular tone generated from within the vascular wall, can be

initiated during hypoxia, tissue hypoperfusion, acidosis, and infusion with vasopressors (86).

5. Tissue oxygenation in the therapeutic context

In tissue oxygenation homeostasis, several therapeutic interventions are available for restoring oxygen delivery to the tissues. These interventions include:

Oxygen therapy: One of the primary interventions for improving tissue oxygenation is administering supplemental oxygen. This therapy is distributed through various delivery systems, including nasal prongs, masks, or high-flow systems, to increase the fraction of inspired oxygen and improve blood oxygen saturation levels (12).

Fluid resuscitation: Adequate fluid resuscitation is critical for restoring tissue oxygenation in patients with hypovolemia or shock (87). Administering intravenous fluids can improve cardiac output and tissue perfusion, improving oxygen delivery to the tissues (88). Administration of vasoactive compounds and fluid therapy are the cornerstones of the hemodynamic management of critically ill patients. Microcirculatory perfusion pressure is the net result of precapillary inflow pressure minus venular outflow pressure (28).

Blood transfusions: Patients with anemia or hemorrhagic shock can receive blood transfusions to augment the oxygen-carrying capability of their blood. This therapy can improve tissue oxygenation by increasing the hemoglobin available to bind and transport oxygen (88).

Vasoactive medications: In some cases, vasoactive drugs such as vasopressors or inotropes may be necessary to improve tissue oxygenation. These medications can improve cardiac output, vascular tone, and tissue blood flow, leading to improved oxygen delivery (58).

There is evidence of abnormal tissue oxygenation in the trapezius muscle of patients with Primary Fibromyalgia (PF), possibly due to microvessel morphological or functional changes. The significantly lower total mean oxygen pressure in the subcutaneous tissue of the patients suggests that PF may affect tissues other than skeletal muscle. The presence of trigger points in painful muscles is a common feature in patients diagnosed with primary fibromyalgia, so acting on these points by massage can be a helpful intervention (89).

Other interventions that can improve tissue oxygenation include correcting electrolyte imbalances, controlling hyperglycemia, and addressing any underlying pathologies contributing to tissue hypoxia. In addition, therapeutic interventions for tissue oxygenation homeostasis should address systemic and local factors. For example, oxygen therapy can improve systemic oxygenation, while local measures such as positioning or pressure-relieving devices can address local factors such as pressure on tissues. Additionally, fluid resuscitation and blood transfusions can improve systemic and local factors by enhancing blood flow and oxygen delivery to tissues (90).

Physical therapy can be an effective approach to improving tissue oxygenation in various pathologies. Exercise training has been shown to enhance the oxygen uptake capacity of muscles and improve overall cardiovascular function, leading to increased tissue oxygenation (91). Additionally, physical therapy techniques such as manual therapy, massage, and stretching can help improve circulation and tissue perfusion, leading to better oxygenation of tissues. Physical therapy can help improve lung function in respiratory pathologies, leading to better blood oxygenation. It is important to individualize physical therapy approaches based on the patient's specific pathology and needs and monitor tissue oxygenation levels during therapy to ensure effectiveness (92).

Hydrotherapy is a therapeutic intervention that uses water to facilitate healing and promote health (8). Hydrotherapy has been shown to positively affect tissue oxygenation, especially in the case of burn injuries, wound healing, and musculoskeletal rehabilitation (93). The buoyancy of the water helps reduce the pressure on the injured area, improving blood flow and tissue oxygenation. Hydrotherapy also reduces pain and swelling,

improving tissue oxygenation by reducing tissue damage and inflammation. In addition, the warmth of the water can promote vasodilation and increase blood flow to the injured area, which can enhance tissue oxygenation (94).

Pelotherapy, the use of mud or clay in medical treatments, has been shown to improve tissue oxygenation in various conditions (9). The heat and pressure generated by applying peloids (mud/clay) can increase blood flow to the affected area, thus increasing tissue oxygenation (95). In addition, the minerals and trace elements found in peloids can have beneficial effects on tissue oxygenation by improving microcirculation and reducing inflammation. Pelotherapy has been used to treat chronic wounds, arthritis, and dermatological conditions such as psoriasis and eczema, with promising results in improving tissue oxygenation and promoting tissue healing. However, further research is needed to fully understand the mechanisms of action and potential benefits of pelotherapy on tissue oxygenation (96).

Therapeutic gases (97) have been used to modulate tissue oxygenation in various clinical conditions (98). For example, hyperbaric oxygen therapy (HBOT) is a treatment that involves inhaling pure oxygen in a pressurized chamber, increasing the amount of oxygen dissolved in the blood, and improving tissue oxygenation in areas with poor perfusion. HBOT has been used in conditions like carbon monoxide poisoning, diabetic ulcers, and radiation-induced tissue damage (99). Inhaled nitric oxide (iNO) is another therapeutic gas that improves tissue oxygenation in acute respiratory distress syndrome (ARDS) and pulmonary hypertension (100). iNO acts as a selective pulmonary vasodilator, improving lung perfusion and oxygenation (101,102).

Carbon monoxide (CO), which is normally toxic, has also been studied for its potential therapeutic effects (103) in improving tissue oxygenation. In low doses, CO has been shown to have anti-inflammatory and cytoprotective effects, improving oxygenation in conditions such as sickle cell disease and acute respiratory distress syndrome (104,105).

Hydrogen sulfide (H_2S) is a gas with various physiological roles and has gained attention for its therapeutic potential (106). Studies have shown that H_2S can improve tissue oxygenation in several pathological conditions, such as ARDS, heart failure, and sepsis. H_2S has been shown to modulate microcirculation, leading to increased oxygen delivery to tissues. It also has antioxidant and anti-inflammatory properties that can prevent cellular damage and maintain cellular function under hypoxic conditions. The therapeutic use of H_2S is still in the experimental phase, and more research is needed to determine its efficacy, safety, and optimal dosing. However, the potential benefits of H2S in improving tissue oxygenation make it a promising area for future research and clinical application (107).

Massage is a therapeutic approach that involves the manipulation of the soft tissues of the body to enhance physical and emotional well-being (108). The mechanical pressure and movements applied during massage can affect tissue oxygenation through various mechanisms, such as increasing blood flow, improving lymphatic circulation, and reducing muscle tension (109). Massage has been shown to improve tissue oxygenation in different populations, including healthy individuals, athletes, and patients with various medical conditions, such as fibromyalgia, chronic low back pain, and cancer (110). In addition, increasing tissue oxygenation after massage can have positive effects, such as reducing pain and inflammation, promoting tissue healing, and improving overall relaxation (111).

Crenotherapy is a type of therapy that involves using mineral waters for various health conditions (112). The use of mineral waters is believed to have beneficial effects on multiple organ systems in the body, including the circulatory and respiratory systems. Some studies suggest that mineral waters can increase tissue oxygenation by improving blood flow and oxygen delivery to the tissues. The minerals present in the water may also have antioxidant effects, which can reduce oxidative stress and improve tissue function (50). Crenotherapy has been used for various conditions, including respiratory diseases, skin conditions, and musculoskeletal disorders. However, more research is needed to

fully understand crenotherapy's mechanisms of action and efficacy for improving tissue oxygenation (113).

Lifestyle factors, such as diet, exercise, smoking, and alcohol consumption, can significantly affect tissue oxygenation levels in the body. For example, a diet rich in fruits, vegetables, and whole grains can provide the body with essential nutrients and antioxidants that help increase oxygen levels (114,115). Regular exercise, on the other hand, improves cardiovascular health and enhances the body's ability to transport and utilize oxygen efficiently. Smoking and alcohol consumption, on the other hand, can decrease tissue oxygenation levels by constricting blood vessels and reducing oxygen-carrying capacity. Thus, modifying lifestyle factors help in maintaining optimal tissue oxygenation levels (116).

Smoking has been shown to have adverse effects on tissue oxygenation and healing. The carbon monoxide in cigarette smoke binds to hemoglobin in the blood, reducing the oxygen level transported to tissues (117). Several studies have shown that smoking is associated with complicated tissue healing and surgical wound complications (118). The proposed mechanism is a reduction in tissue blood flow and oxygen. An ample oxygen supply is fundamental to wound healing, as it facilitates the growth of new blood vessels and the formation of new tissue.

Additionally, avoiding or managing conditions such as obesity, diabetes, and hypertension can also improve tissue oxygenation and reduce the risk of tissue hypoxia. Prophylactic measures such as supplemental oxygen therapy may be necessary for specific high-risk populations to prevent tissue hypoxia. For example, individuals undergoing surgery or with severe respiratory diseases may require oxygen supplementation to ensure adequate tissue oxygenation (119).

Regular health check-ups and monitoring of tissue oxygenation levels may also be necessary for individuals at high risk of developing tissue hypoxia. This includes individuals with cardiovascular or respiratory diseases, anemia, or tissue hypoxia history. In summary, several preventive measures and prophylactic interventions can be taken to improve tissue oxygenation and reduce the risk of tissue hypoxia. Maintaining a healthy lifestyle, avoiding exposure to toxins, and managing underlying medical conditions is essential to maintaining proper tissue oxygenation levels (120).

6. Results seen as progress in the last two years resulting from PRISMA-type systematic review

6.1. Data regarding monitoring of microcirculation and tissue oxygenation level

In clinical management, it is vital to maintain optimal hemodynamics by ensuring adequate tissue oxygenation at the microcirculatory level. However, we often rely on macro-hemodynamic variables such as blood pressure and heart rate, neglecting microcirculation. Technologies assessing tissue oxygenation or microcirculatory blood flow have been developed and incorporated into clinical practice to address this issue (2).

Near-infrared spectroscopy (NIRS) is a noninvasive technique for measuring tissue oxygenation (121), which can monitor tissue perfusion in shock by revealing tissue hemoglobin oxygen saturation (StO2) (122). Monitoring tissue perfusion and oxygenation is crucial to managing sepsis-related circulatory dysfunction. However, sepsis-related tissue edema can affect the accuracy of NIRS measurements, and further investigation is needed to determine the impact of tissue water on NIRS measurements (123).

Near-infrared spectroscopy (NIRS) and diffuse correlation spectroscopy (DCS) can be used to measure cerebral hemodynamics, which can be used to assess the cerebral metabolic rate of oxygen and cerebral autoregulation (124). NIRS is now validated as a noninvasive method to measure tissue oxygenation (125). Tissue oxygenation can be monitored using a NIRS-based tissue oximeter (126). NIRS is a technique that measures the absorption of oxyhemoglobin, deoxyhemoglobin, and cytochrome C oxidase. NIRS has been used to study cerebral physiology, focusing on hemoglobin absorption (127). NIRS is an optical technology that provides continuous measurements of tissue hemodynamics

and oxygenation and can be a reliable method for continuous monitoring of pulmonary function in patients with acute pneumonia. This technology can provide several benefits, including triaging infected patients, monitoring disease progression and responses to treatment, and early detection of acute pneumonia (128). In addition, portable NIRS devices in ambulances could help evaluate cerebral blood perfusion and improve the rate of ROSC through increased oxygen delivery to the brain (129).

Researchers have developed a time-domain near-infrared spectroscopy (TD-NIRS) system that utilizes a supercontinuum light source and multi-wavelength detection. This system can monitor tissue oxygenation in real time and is designed for use in clinical settings. TD-NIRS provides more information than other acquisition modes and can help diagnose physiological conditions and monitor clinical interventions. Recent developments in optical technologies and electronics have enabled better measurements and broader applications for TD-NIRS, including larger source-detector separations, longer wavelengths, more sources and detectors, and more compact and wearable designs. Advancements also involve integrating various imaging techniques with TD-NIRS (130).

Hyperspectral imaging (HSI) is a noninvasive method to estimate SO2 near the affected area. Various algorithms have been developed for SO2 estimation from hyperspectral information and have found their way into clinical devices. However, some researchers have noted discrepancies in SO2 estimation accuracies for different skin types, with higher errors seen for patients with higher melanin concentration (i.e., darker skin) (131). HSI is an emerging technique that measures tissue oxygenation by analyzing concentrations of OxyHb and DeoxyHb. The new HyperView™ HSI device is handheld and can measure tissue oxygenation at any location on the lower extremity (132).

In recent years, Blood oxygen level-dependent magnetic resonance imaging (BOLD-MRI) has become a standard technique for assessing changes in tissue oxygenation (133). The use of physiological markers to complement intracranial pressure (ICP) measurements in detecting cerebral hypoxia and preventing adverse events has been proposed. Brain tissue oxygenation (PbtO2) is a potential marker that has been studied, and a decrease in PbtO2 below 10 mmHg has been associated with poor outcomes. However, optimal thresholds for PbtO2 remain controversial, and interpretation varies depending on placement location and pathology (134). Bedside brain tissue oxygen monitoring (BTOM) is crucial for managing comatose patients with acute brain injuries to prevent secondary ischemia. The Licox probe is the preferred tool for BTOM due to its stability and lack of competition. However, traditional implantation methods involving metal bolts can cause significant MRI artifacts, making targeting the desired area of the brain parenchyma difficult. A new technique involving a peripheral venous cannula and a plastic bolt from a different vendor has been developed to address this issue, allowing for adjustable insertion length and rigid fixation without causing metal artifacts in early MRI (135).

In tumors, low oxygen concentration, or hypoxia, affects their growth and response to anticancer drugs. Oxygen distribution in tumors is nonuniform and varies due to the atypical structure of tumor blood vessels, which can affect the effectiveness of treatments such as photodynamic therapy. Invasive polarographic methods are commonly used to determine tissue oxygen status, but noninvasive methods using luminescent sensors have also been developed. Sensors based on luminescence are based on luminescence quenching by molecular oxygen, including trypafavine, eosin, erythrosine, and metalloporphyrins. Oxygen-dependent phosphorescence and oxygen-independent fluorescence can be used to avoid concentration variations (136). A study has developed an in silico tumor model to simulate realistic 3D microvascular structures and related oxygenation maps. The model features regions with different levels and typologies of hypoxia and could be integrated into a treatment planning system to evaluate and compare various scenarios when deciding the therapy to administer. Tumor oxygenation is an essential factor influencing the response of cells to radiation and chemo therapies, and this model allows for simulations of key radiobiological features governing the tumor response to radio- and

chemotherapy. The model also distinguishes between different types of hypoxia on a cellular scale, which is essential in assessing the response of cells to radiotherapy (137).

A minimally invasive wireless implantable luminescence oxygen sensor has been developed to monitor deep-tissue oxygenation in organ transplantation patients. This system provides real-time data and reports continuous tissue oxygenation monitoring from centimeter-scale depths. The method comprises a millimeter-sized, ultrasound-powered implantable luminescence O2 sensor and an external transceiver for bidirectional data transfer, enabling deep-tissue oxygenation monitoring for surgical or critical care indications. In addition, the system is expected to help differentiate parenchymal rejection from vascular graft disease in graft dysfunction (138).

Blood plays a crucial role in providing oxygen to organs during exercise and in heat regulation for body temperature stabilization. A study used a three-wavelength frequency-domain diffuse reflectance spectroscopy (FD DRS) system to investigate the hemodynamic oxygenation in the forearm's skin tissue during exercise, monitoring heartbeat rate and skin temperature. The study found changes in the concentration of oxygenated/deoxygenated hemoglobin molecules, total hemoglobin concentration, and skin temperature. The FD DRS system helps analyze athletes' physiological status and may enable wearable design (139).

6.2. New data regarding tissue oxygenation in various pathological circumstances

Various disease processes, particularly diabetes mellitus, are associated with cellular hypoxia. This can be caused by factors such as the impaired release of oxygen from hemoglobin, slowed hemoglobin oxygen saturation, defective mitochondrial oxidative phosphorylation, and impaired insulin signaling. Hyperbaric oxygen therapy can improve tissue oxygenation and insulin sensitivity, but it is not practical for the long-term management of diabetes. Drinking oxygen-enriched water may be a viable option for oxygen supplementation, as oxygen can be absorbed into the circulation from the gastrointestinal tract. The study investigated the effects of oxygen-enriched bottled drinking water on arterial oxygen levels and mitochondrial function in cultured cells (140).

Patients undergoing major spine surgery are at risk of postoperative complications, including covert stroke and myocardial infarction, which can be asymptomatic. Intraoperative tissue oxygen desaturation is expected due to significant blood loss and hemodynamic changes during major spine surgeries (141). In addition, the oxygen level in microcirculatory tissues is related to kidney function after transcatheter aortic valve implantation (142).

Drag-reducing polymers can modulate hemorheological mechanisms by increasing arteriolar blood volume flow and reducing pressure loss across the arterial network. These mechanisms lead to an increase in precapillary blood pressure, enhancing capillary perfusion and improving tissue oxygenation. Drag-reducing polymers resuscitation fluids can restore adequate capillary perfusion to maintain homeostasis, remove metabolic waste products, and overcome deficits in oxygen delivery (143).

Sufficient oxygenation is crucial for wound healing, and lack of it can lead to ulcers. Chronic Venous Insufficiency (CVI) can impair microcirculation, leading to skin changes and ulcer formation. However, the correlation between CVI and tissue oxygenation is unclear, and TcPO2 measurement can help predict wound healing. In this study, TcPO2 in advanced CVI stages was compared to the unaffected limb to understand better the disease process, prognosis, and effectiveness of treatments. The hypothesis was that tissue oxygenation progressively decreases with CVI severity (144).

Diabetic foot callus increases the risk of ulcers, and scalpel debridement is a standard procedure to remove dead tissue. However, the outcome may depend on the clinician's experience. Therefore, tissue oxygenation measurements are obtained before and after the procedure to standardize the process and study its effects on callus tissue (145).

Radiation dermatitis (RD) is a common adverse reaction experienced by over 95% of breast cancer patients undergoing radiation therapy (RT). Non-contact near-infrared

spectroscopy (NIRS) based imaging was used to correlate sub-clinical tissue oxygenation changes with RD grading in irradiated and surrounding non-irradiated tissues in breast cancer patients undergoing RT. Was found a negative correlation between the severity of RD and tissue oxygen saturation, with a drop in saturation correlated with increased severity of RD. Pre-RT assessment of tissue oxygen saturation could predict the risk of adverse reactions during RT, while post-RT assessment could be used to monitor recovery (146).

Older patients with vasovagal syncope and orthostatic hypotension seem to tolerate deoxygenation during orthostatic provocation better than younger patients, which could be explained by the shorter cerebral anoxia reserve time in young individuals. However, further research is needed to study the cognitive function concerning deoxygenation during the presyncopal phase (147).

6.3. New data regarding tissue oxygenation in the therapeutic context

The use of blood laser irradiation improves tissue oxygenation and enhances the morphofunctional activity of blood, with energetic effects comparable to antibiotics. Combining blood laser irradiation with oral or intramuscular antibiotic administration leads to higher drug saturation in the blood compared to intramuscular injection alone. In addition, this technique accelerates functional restoration, stimulates adaptational ability, and stabilizes the hormonal state (148).

Photodynamic therapy (PDT) is a practical approach for dealing with drug-resistant bacterial infections, but it is challenging to implement in hypoxic environments found in intractable disorders like refractory keratitis and periodontitis. Algae oxygen generation under light irradiation is a promising solution to increase oxygen supply, especially for chronic infections. Modified cyanobacteria have been developed to enhance oxygen production and photodynamic generation of free radicals, thereby improving bacteria elimination and biofilm removal (149).

Efficient wound healing requires coordinated processes in skin cell migration and adhesion. Gas plasma technology promotes skin regeneration through the generation of therapeutic reactive species. However, the underlying molecular mechanisms that regulate gas plasma-aided cell adhesion and matrix remodeling are unclear. In vitro and in vivo studies showed that gas plasma exposure changed the phosphorylation of signaling molecules and affected adhesion receptors, structural proteins, and gene transcription associated with wound healing. Gas plasma exposure also increased tissue oxygenation and skin perfusion during wound healing. These results provide insights into the molecular machinery of gas plasma-assisted wound healing mechanisms (150).

Guiding therapy based on brain tissue oxygenation (PbtO2) can improve neurological outcomes in patients with traumatic brain injury (151). PbtO2 monitoring provides essential information about tissue oxygenation, which can help initiate therapies even when normal intracranial pressure values. Brain oxygen values balance oxygen delivery, consumption, and extraction (151).

Recently, researchers have explored photosynthetic microalgae as a source of oxygen in tissue engineering. Studies have shown that microalgae, such as *Chlorella sorokiniana* and *Chlamydomonas reinhardtii*, can generate sufficient oxygen for tissue constructs under in vitro anoxic conditions. Different methods have been used, such as co-encapsulating microalgae and cells in alginate beads or collagen scaffolds and 3D bioprinting microalgae and cells (152). One of the challenges in tissue engineering is controlling the oxygen supply to cells for their survival and differentiation. A noninvasive optical method using oxygen-sensitive microbeads embedded in 3D-printed cellular constructs allows the mapping of oxygen tension in cellular microenvironments. Oxygen levels can be controlled through blueprint design, and monitoring over time allows control over tissue construct development. This method can be used to time a switch from growth to differentiation media when desired oxygen microenvironments are achieved (153).

The use of cold plasma treatment in wound healing increases oxygen delivery and supports tissue angiogenesis. Using hyperspectral imaging (HSI), researchers could detect a significant difference in absorption spectra between plasma-treated and untreated wounds during the early and late phases of healing. HSI showed increased oxygen saturation, perfusion, and hemoglobin concentration and decreased water content in plasma-treated wounds (41). HSI was able to detect changes in tissue oxygenation and perfusion during shock and assess resuscitation effectiveness. It also showed that skin oxygenation measurements could reflect kidney function, indicating the potential to monitor skin microcirculatory changes during circulatory compromise to assess organ oxygenation. HSI parameters could be used for tissue-perfusion-guided therapy. The combined evaluation of tissue oxygenation, hemoglobin, and water content could open up new possibilities for hemodynamic management guidance, requiring future interventional trials for validation (154).

During high-intensity exercise, hyperventilation can lead to hypocapnia and cause cerebral vasoconstriction, reducing cerebral oxygen delivery and tissue oxygenation. Tibetans may have superior aerobic performance due to their ability to maintain higher cerebral tissue oxygenation in normoxia. Studies have found that Tibetans have a tremendous increase in internal carotid artery blood velocity and estimated cerebral oxygen delivery during exercise compared to Han Chinese, but the effect of hypoxia on cerebral perfusion response varies among populations (155).

Plyometric exercises use anaerobic energy metabolism and rely on the phosphagen system for high-intensity exercise. Oxygen availability plays a critical role in the resynthesis of high-energy phosphates required for muscle recovery. After a plyometric training session, muscle oxygen desaturation was observed, and recovery was complete within one minute. The recovery time for muscle re-oxygenation may depend on exercise mode and intensity (156).

Cerebral oxygenation is protected post-orthostasis at high altitudes, while peripheral oxygenation is reduced. This indicates a different regulation in the cerebral and peripheral circulations and suggests an adaptive response to maintain cerebral oxygenation during orthostasis at high altitudes. Short-term acclimatization did not change the oxygenation response (157).

Hypoxemia and hypoxia can occur in low-oxygen or low-pressure environments, reducing tissue oxygen saturation. Hypoxic hypoxia, resulting from low pressure, is common in mountaineering, aviation, and military activities. Normobaric hypoxia, achieved through reduced FiO2, is used in research to examine the physiological and cognitive effects of hypoxia. Near-infrared spectroscopy measures peripheral tissue oxygen saturation (StO2), which can detect fatigue- and dose-dependent changes in hypoxic-related tissue saturation. In addition, psychomotor vigilance testing (PVT) is used to assess cognitive function and reaction time under hypoxic and fatigued conditions. Combining physiological and cognitive measures can provide valuable information for mission planning and countermeasure development in high-stress activities.

Hyperbaric oxygen treatment (HBO) increases the dissolved oxygen in the blood and can have therapeutic effects, but its impact on tissue blood flow has been under-researched. Peripheral blood flow decreased early in the HBO exposure but increased as the exposure continued. Fluctuations in peripheral blood flow were more significant in the limbs than in the ear, possibly due to environmental factors (158).

7. Meta-Analysis

Based on the PICOT analysis, the studies can be compared and evaluated based on their ability to accurately and reliably measure tissue oxygenation or cerebral oximetry in adult patients with vascular or neurological disorders who require monitoring.

Population: Adult patients with vascular or neurological disorders who require tissue oxygenation or cerebral oximetry monitoring.

Intervention: Various monitoring devices are used to measure tissue oxygenation or cerebral oximetry, including vacuum suspension, O3 regional somatic tissue oxygenation monitor, near-infrared spectroscopy, brain oxygenation monitor, and Nonin 4 wavelength cerebral oximeter.

Comparison: There may not be a direct comparison between the devices used in each study, but they can be compared based on their efficacy in measuring tissue oxygenation or cerebral oximetry.

Outcome: The primary outcome is the accuracy and reliability of the different monitoring devices in measuring tissue oxygenation or cerebral oximetry.

Time: The studies can be conducted over several months to years, depending on the number of participants and the monitoring device used.

Table 2. Studies selected after searching for completed studies by "tissue oxygenation" on https://clinicaltrials.gov/.

No	Study Title	Conditions	Interventions	Study Design	Outcome Measures	Number Enrolled	NCT No.
1	Vacuum Suspension: Effects on Tissue Oxygenation, Activity and Fit	Amputation Diabetes Leg Injuries Traumatic Amput	Device: Total Surface Bearing Suction Socket Device: Vacuum assisted socket system	Allocation: Randomized Intervention Model: Crossover Masking: Single (Participant) Primary Purpose: Treatment	Limb Volume Activity Level Limb Pistoning (and 3 more...)	20	NCT00117793
2	Validation of the O3 Regional Somatic Tissue Oxygenation Monitor	Oxygen Deficiency	Device: Masimo O3 Regional Oximeter	Allocation: N/A Intervention Model: Single Group Masking: None (Open Label) Primary Purpose: Other	Accuracy of O3 Sensor by ARMS Calculation of Percent rSO2	37	NCT04584788
3	Nitrites, Exercise, and Peripheral Arterial Disease NO-PAD	Peripheral Arterial Disease	Drug: Beetroot Juice & Supervised Exercise Training Other: Placebo Comparator Beverage & Exercise Training	Allocation: Randomized Intervention Model: Parallel Masking: Triple (Participant, Care Provider, Outcomes Assessor) Primary Purpose: Treatment	Change in Exercise Capacity: VO2peak (Maximal O2 Cons.) Change In Time To Exhaustion Change in Functional Ability (and 3 more...)	32	NCT01684930
4	Comparison of Two Devices Using Near-infra Red Spectroscopy During a Vascular Occlusion Test	Healthy	Device: vascular occlusion test	Allocation: N/A Intervention Model: Single Group Masking: Double (Investigator, Outcomes Assessor) Primary Purpose: Diagnostic	Change of Tissue Oxygenation Value During Ischemia and Reperfusion	20	NCT01848977
5	CURES: The Effect of Deep Curarisation and Reversal With Sugammadex on Surgical Conditions and Perioperative Morbidity	Obesity Laparoscopic Gastric Bypass Surgery Surgical Conditions (and 2 more...)	Drug: deep neuromuscular blockade with rocuronium, reversal with sugammadex Drug: normal neuromuscular blockade reversal with rocuronium,	Allocation: Randomized Intervention Model: Parallel Masking: Triple (Participant, Investigator, Outcomes Assessor) Primary Purpose: Supportive Care	Subjective Evaluation of the View on the Operating Field Surgeon Number of Intra-abdominal Pressure Rises > 18cmH2O Duration of Surgery (and 3 more...)	60	NCT01748643
6	Validation of Brain Oxygenation Monitor	Healthy	Device: Desaturation	Allocation: N/A	Accuracy of Sensor	18	NCT00815490

				Intervention Model: Single Group Masking: None (Open Label) Primary Purpose: Diagnostic			
7	Nonin 4 Wavelength Cerebral Oximeter Study	Healthy	Device: Reduction of inspired oxygen	Allocation: N/A Intervention Model: Single Group Masking: None (Open Label) Primary Purpose: Diagnostic	Accuracy of Sensor	23	NCT01762722
8	Brain Oxygenation and Hemodynamics During Sleep in Obstructive Sleep Apnea Sufferers NIRS-OSAS	Obstructive Sleep Apnea Syndrome	Device: OxiplexTS	Allocation: Non-Randomized Intervention Model: Parallel Masking: None (Open Label) Primary Purpose: Diagnostic	Percentage of Oxygen Saturation in the Brain During Sleep Oxyhemoglobin Concentration in the Brain During Sleep Total Hemoglobin Concentration in the Brain During Sleep (and 2 more...)	309	NCT00591591

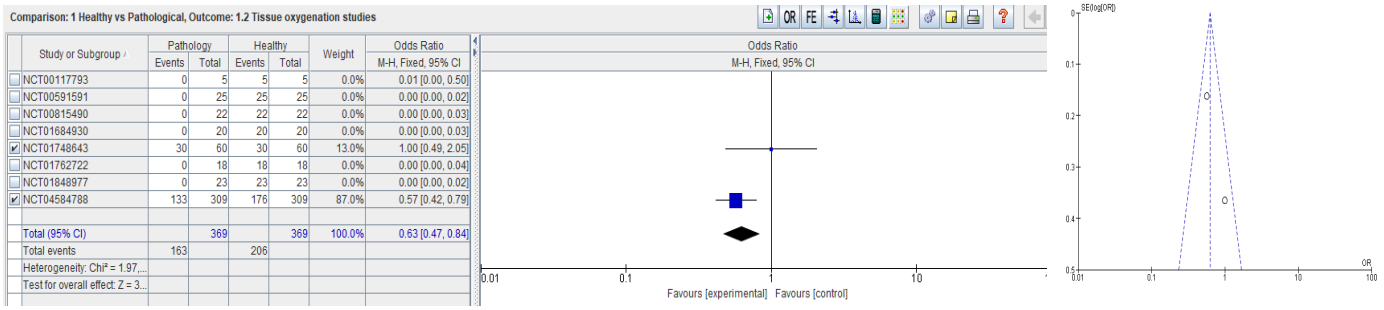

Figure 3. Meta-Analysis regarding the dichotomic outcome of patients vs. healthy subjects.

8. Discussion

Discuss the current understanding of tissue oxygenation homeostasis

Tissue oxygenation homeostasis is a delicate balance between oxygen supply and demand within cells and tissues. The current understanding is that adequate tissue oxygenation is necessary for the normal functioning of cells and organs and that tissue hypoxia can lead to a range of pathological conditions. The primary mechanism for maintaining tissue oxygenation is through the delivery of oxygen by the circulatory system. Oxygen is transported in the blood by hemoglobin, and a complex interplay of factors, including blood flow, cardiac output, oxygen saturation, and tissue perfusion, regulate oxygen delivery. In addition, the cellular mechanisms that regulate oxygen utilization, such as the activity of mitochondrial enzymes, play a critical role in maintaining tissue oxygenation homeostasis (159).

Tissue oxygenation homeostasis is critical in maintaining normal physiological function in the human body. In healthy individuals, oxygen supply to tissues is regulated by a complex interplay between the cardiovascular and respiratory systems. The partial pressure of oxygen in the arterial blood is the primary determinant of oxygen delivery to tissues, which is influenced by several factors, such as blood flow, hemoglobin concentration, and tissue oxygen consumption. In pathophysiological circumstances, tissue oxygenation homeostasis can be altered due to various factors, such as decreased oxygen supply, increased oxygen demand, and impaired oxygen utilization. For example, in conditions like ischemia, hypoxia, or shock, the body's ability to supply oxygen to tissues may be compromised, leading to tissue damage and dysfunction. In addition, therapeutic

interventions can also affect tissue oxygenation homeostasis. For instance, administering supplemental oxygen, mechanical ventilation, or vasoactive drugs may improve tissue oxygenation in certain conditions. However, these interventions can also have adverse effects, such as oxygen toxicity, impaired microcirculation, or tissue damage (160).

The microcirculatory system is essential to the human body's circulatory system. It delivers oxygen and nutrients to the cells and removes metabolic waste. It is also the site of many physiological processes, including autoregulation, vasomotion, and capillary filtration. Microcirculation impairment is associated with various diseases and disorders, including diabetes, systemic sclerosis, multiple organ dysfunction syndrome, and trauma. In addition, smoking and obesity can also affect microcirculation, leading to an increased risk of tissue injury and impaired wound healing (161).

The systematic review article presents current data regarding the homeostasis of tissue oxygenation in pathophysiological and therapeutic circumstances. The findings of the selected studies suggest that various factors influence tissue oxygenation and are highly context-dependent. The review highlights the importance of understanding the underlying mechanisms of tissue oxygenation homeostasis in different physiological and pathological conditions, as this knowledge can guide the development of targeted interventions to improve tissue oxygenation and prevent tissue damage. Additionally, the review highlights the need for further research to understand better the complex interplay between oxygen supply, utilization, and demand in tissues and to develop more effective therapeutic strategies to maintain tissue oxygenation homeostasis in diverse clinical contexts.

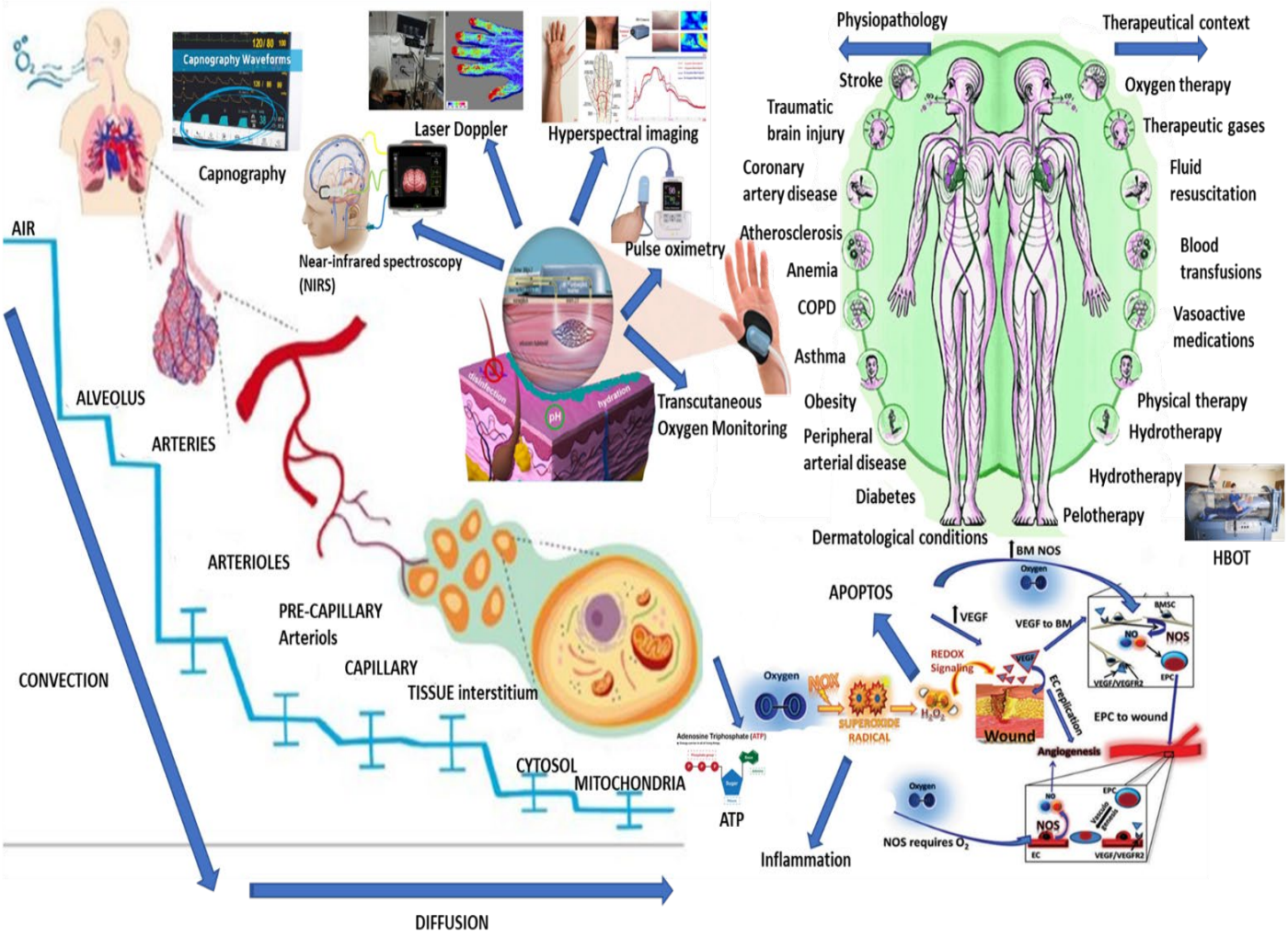

Figure 4. The complex levels of tissue oxygenation homeostasis analysis and measurement methods.

There have been significant scientific advances in the field of tissue oxygenation homeostasis in recent years. These include the development of new technologies for measuring tissue oxygenation, such as near-infrared spectroscopy and polarography, which provide more accurate and detailed information about tissue oxygen levels. Additionally, studies have uncovered new mechanisms by which the body regulates tissue oxygenation, including the role of microvascular networks and angiogenesis. The discovery of hypoxia-inducible factor (HIF) has also been a significant advance, as it plays a crucial role in regulating the body's response to low oxygen levels. Finally, there have been advances in the use of oxygen therapies, such as hyperbaric oxygen therapy and normobaric oxygen therapy, which have been shown to improve tissue oxygenation in various conditions (162).

Although there has been significant progress in our understanding of tissue oxygenation homeostasis, there are still gaps in our knowledge. One significant gap is the lack of comprehensive studies on the molecular mechanisms underlying tissue oxygenation regulation, particularly in different pathological conditions. Additionally, there is a need for more studies on the effects of environmental factors on tissue oxygenation, such as temperature, humidity, and altitude. Another gap is the limited understanding of the interactions between tissue oxygenation and the immune system, especially in inflammation and infection. Finally, there is a need for more research on the impact of lifestyle factors, such as diet and exercise, on tissue oxygenation homeostasis (163).

One of the limitations of current research methods in studying tissue oxygenation homeostasis is the invasive nature of some techniques used to measure tissue oxygen levels (164). For instance, using oxygen-sensitive electrodes or microelectrodes, while precise, requires the insertion of a probe into the tissue, which can damage and alter the tissue oxygenation levels. Additionally, the use of animal models to study tissue oxygenation homeostasis may not fully translate to human physiology due to inter-species differences. Furthermore, the current understanding of tissue oxygenation homeostasis is mainly limited to a few organs, such as the brain and heart, and more research is needed to understand tissue oxygenation in other organs and tissues. Finally, some of the current research is limited to specific pathological conditions, and more studies are required in order to fully understand the dynamics of tissue oxygenation homeostasis in healthy individuals (165).

9. Conclusions

Living systems are autonomous and complex and exist in a state of bounded instability in which there is an ever-present dynamic balance between order and disorder at the edge of chaos. Living systems are open to their environment, interact with it, and have information, energy, and physical material flows with it. Various therapeutic interventions are available for restoring tissue oxygenation homeostasis. The choice of intervention will depend on the underlying pathology, the severity of the tissue hypoxia, and the patient's clinical status. Monitoring tissue oxygenation parameters and adjusting therapy to achieve optimal tissue oxygenation levels is essential. A holistic approach to tissue oxygenation homeostasis involves addressing systemic and local factors contributing to oxygenation. Systemic factors include adequate ventilation and oxygenation, sufficient cardiac output, and appropriate hemoglobin levels. Local factors include maintaining adequate microcirculation, avoiding pressure on tissues, and addressing any underlying tissue damage or inflammation.

In conclusion, tissue oxygenation homeostasis is critical to maintaining normal physiological function in the human body. The understanding of tissue oxygenation has advanced significantly in recent years thanks to advances in technology and research. However, gaps in our knowledge and limitations of current research methods still need to be addressed. Therefore, future research in this area should focus on exploring the molecular mechanisms of tissue oxygenation, developing novel therapeutic interventions to optimize tissue oxygenation, and managing the gaps in our knowledge of tissue oxygenation in specific pathological conditions.

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References

1. Jacob M, Chappell D, Becker BF. Regulation of blood flow and volume exchange across the microcirculation. Crit Care [Internet]. 2016;20(1):1–13. Available from: http://dx.doi.org/10.1186/s13054-016-1485-0
2. de Keijzer IN, Massari D, Sahinovic M, Flick M, Vos JJ, Scheeren TWL. What is new in microcirculation and tissue oxygenation monitoring? J Clin Monit Comput [Internet]. 2022;36(2):291–9. Available from: https://doi.org/10.1007/s10877-022-00837-x
3. Samsel RW, Schumacker PT. Oxygen delivery to tissues. Eur Respir J. 1991;4(10):1258–67.
4. Charlton M, Sims M, Coats T, Thompson JP. The microcirculation and its measurement in sepsis. J Intensive Care Soc. 2017;18(3):221–7.
5. Hachmo Y, Hadanny A, Mendelovic S, Hillman P, Shapira E, Landau G, et al. The effect of hyperbaric oxygen therapy on the pathophysiology of skin aging: a prospective clinical trial. Aging (Albany NY). 2021;13(22):24500–10.
6. Olascoaga A, Vilar-Compte D, Poitevin-Chacón A, Contreras-Ruiz J. Wound healing in radiated skin: Pathophysiology and treatment options. Int Wound J. 2008;5(2):246–57.
7. Frontera WR. DeLisa's physical medicine and rehabilitation: Principles and practice: Fifth edition. Vols. 1–2, DeLisa's Physical Medicine and Rehabilitation: Principles and Practice: Fifth Edition. 2012. 1–2432 p.
8. Munteanu Constantin DM. Hydrotherapy. Balneo-Research J. 2012;3(1):23–7.
9. Munteanu C, Rotariu M, Dogaru G, Ionescu VE, Vlad C, Onose G. Mud therapy and rehabilitation - scientific relevance in the last six years (2015 – 2020) Systematic literature review and meta-analysis based on the PRISMA paradigm. Balneo PRM Res J. 2021;12(1):1–15.
10. Chen Q, Wang Q, Zhu J, Xiao Q, Zhang L. Reactive oxygen species: key regulators in vascular health and diseases. Br J Pharmacol. 2018;175(8):1279–92.
11. Van Damme N, Van Hecke A, Remue E, Van den Bussche K, Moore Z, Gefen A, et al. Physiological processes of inflammation and edema initiated by sustained mechanical loading in subcutaneous tissues: A scoping review. Wound Repair Regen. 2020;28(2):242–65.
12. Avraham M, Meirovithz E. Oxygen Homeostasis and Mitochondrial Function in COVID-19 and ARDS Patients: The Ultimate Vital Signs. J Biosci Biomed Eng ISSN 2693-2504. 2020;1(3):1–24.
13. Redza-Dutordoir M, Averill-Bates DA. Activation of apoptosis signalling pathways by reactive oxygen species. Biochim Biophys Acta - Mol Cell Res [Internet]. 2016;1863(12):2977–92. Available from: http://dx.doi.org/10.1016/j.bbamcr.2016.09.012
14. Leach RM, Treacher DF. The pulmonary physician in critical care · 2: Oxygen delivery and consumption in the critically ill. Thorax. 2002;57(2):170–7.
15. Dominelli PB, Wiggins CC, Roy TK, Secomb TW, Curry TB, Joyner MJ. The Oxygen Cascade During Exercise in

Health and Disease. Mayo Clin Proc [Internet]. 2021;96(4):1017–32. Available from: https://doi.org/10.1016/j.mayocp.2020.06.063

16. Munteanu C, Rotariu M, Turnea MA, Anghelescu A, Albadi I, Dogaru G, Silișteanu SC, Ionescu EV, Firan FC, Ionescu AM, Oprea C OG. Topical Reappraisal of Molecular Pharmacological Approaches to Endothelial Dysfunction in Diabetes Mellitus Angiopathy. Curr Issues Mol Biol 2022 Jul 28;44(8)3378-3397 doi 103390/cimb44080233 PMID 36005129; PMCID PMC9406839.
17. Beyer C, Schett G, Gay S, Distler O, Distler JHW. Hypoxia. Hypoxia in the pathogenesis of systemic sclerosis. Arthritis Res Ther. 2009;11(2):220.
18. Wei YH, Lu CY, Wei CY, Ma YS, Lee HC. Oxidative stress in human aging and mitochondrial disease-consequences of defective mitochondrial respiration and impaired antioxidant enzyme system. Chin J Physiol. 2001;44(1):1–11.
19. Ortiz-Prado E, Dunn JF, Vasconez J, Castillo D, Viscor G. Partial pressure of oxygen in the human body: a general review. Am J Blood Res [Internet]. 2019;9(1):1–14. Available from: http://www.ncbi.nlm.nih.gov/pubmed/30899601%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC6420699
20. Assuncao MS antucc. C de, Corrêa TD omingo., Bravim B de A, Silva E. How to choose the therapeutic goals to improve tissue perfusion in septic shock. Einstein (Sao Paulo). 2015;13(3):441–7.
21. Stoica SI, Bleotu C, Ciobanu V, Ionescu AM, Albadi I, Onose G, et al. Considerations about Hypoxic Changes in Neuraxis Tissue Injuries and Recovery. Biomedicines. 2022;10(2):1–19.
22. Shi H, Liu KJ. Cerebral tissue oxygenation and oxidative brain injury during ischemia and reperfusion. Front Biosci 12, 1318-1328, January 1, 2007.
23. Pries AR, Secomb TW, Gaehtgens P. The endothelial surface layer. Pflugers Arch Eur J Physiol. 2000;440(5):653–66.
24. Page MJ, Moher D, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. PRISMA 2020 explanation and elaboration: Updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372.
25. Berthon P, Nairn A, Money A. Through the Paradigm Funnel: A Conceptual Tool for Literature Analysis. Mark Educ Rev. 2003;13(2):55–66.
26. van der Willik EM, van Zwet EW, Hoekstra T, van Ittersum FJ, Hemmelder MH, Zoccali C, et al. Funnel plots of patient-reported outcomes to evaluate health-care quality: Basic principles, pitfalls and considerations. Nephrology. 2021;26(2):95–104.
27. Finch PM. The evidence funnel: Highlighting the importance of research literacy in the delivery of evidence informed complementary health care. J Bodyw Mov Ther. 2007;11(1):78–81.
28. Boerma EC, Ince C. The role of vasoactive agents in the resuscitation of microvascular perfusion and tissue oxygenation in critically ill patients. Intensive Care Med. 2010;36(12):2004–18.
29. Nitzan M, Nitzan I, Arieli Y. The various oximetric techniques used for the evaluation of blood oxygenation. Sensors (Switzerland). 2020;20(17):1–28.
30. Hofmann J, Meier RJ, Mahnke A, Schatz V, Brackmann F, Trollmann R, et al. Ratiometric luminescence 2D in vivo imaging and monitoring of mouse skin oxygenation. Methods Appl Fluoresc. 2013;1(4).
31. Ganesan G, Leu S, Cerussi A, Tromberg B, Cooper DM, Galassetti P. Cerebral and Muscle Tissue Oxygenation During Incremental Cycling in Male Adolescents Measured by Time-Resolved NIRS. Pediatr Exerc Sci 2016 May ; 28(2) 275–285 doi101123/pes2015-0037.
32. Kuliga KZ, Mcdonald EF, Gush R, Michel C, Chipperfield AJ, Clough GF. Dynamics of Microvascular Blood Flow and Oxygenation Measured Simultaneously in Human Skin. Microcirculation. 2014;21(6):562–73.

33. Davis SL, Fadel PJ, Cui J, Thomas GD, Crandall CG. Skin blood flow influences near-infrared spectroscopy-derived measurements of tissue oxygenation during heat stress. J Appl Physiol. 2006;100(1):221–4.
34. Forst T, Hohberg C, Tarakci E, Forst S, Kanna P, Pfützner A. Reliability of lightguide spectrophotometry (O2C®) for the investigation of Skin tissue microvascular blood flow and tissue oxygen supply in diabetic and nondiabetic subjects. J Diabetes Sci Technol. 2008;2(6):1151–6.
35. Salminen A V., Rimpilä V, Polo O. Peripheral hypoxia in restless legs syndrome (Willis-Ekbom disease). Neurology. 2014;82(21):1856–61.
36. Kmiec MM, Hou H, Lakshmi Kuppusamy M, Drews TM, Prabhat AM, Petryakov S V., et al. Transcutaneous oxygen measurement in humans using a paramagnetic skin adhesive film. Magn Reson Med. 2019;81(2):781–94.
37. Christen T, Bouzat P, Pannetier N, Coquery N, Moisan A, Lemasson B, et al. Tissue oxygen saturation mapping with magnetic resonance imaging. J Cereb Blood Flow Metab. 2014;34(9):1550–7.
38. Shellock FG, Fleckenstein JL. Muscle physiology and pathophysiology: Magnetic resonance imaging evaluation. Semin Musculoskelet Radiol. 2000;4(4):459–79.
39. Lopes De Miranda M, Balarini M, Caixeta D, Bouskela E. Microcirculatory dysfunction in sepsis: Pathophysiology, clinical monitoring, and potential therapies. Am J Physiol - Hear Circ Physiol. 2016;311(1):H24–35.
40. Zuzak KJ, Gladwin MT, Cannon RO, Levin IW. Imaging hemoglobin oxygen saturation in sickle cell disease patients using noninvasive visible reflectance hyperspectral techniques: Effects of nitric oxide. Am J Physiol - Hear Circ Physiol. 2003;285(3 54-3):1183–9.
41. Schmidt A, Niesner F, Von Woedtke T, Bekeschus S. Hyperspectral Imaging of Wounds Reveals Augmented Tissue Oxygenation following Cold Physical Plasma Treatment in Vivo. IEEE Trans Radiat Plasma Med Sci. 2021;5(3):412–9.
42. Chin MS, Freniere BB, Lo Y-C, Saleeby JH, Baker SP, Strom HM, et al. Hyperspectral imaging for early detection of oxygenation and perfusion changes in irradiated skin. J Biomed Opt. 2012;17(2):026010.
43. Philimon SP, Huong AKC, Ngu XTI. Tissue oxygen level in acute and chronic wound: A comparison study. J Teknol. 2020;82(4):131–40.
44. Michiels C. Physiological and pathological responses to hypoxia. Am J Pathol. 2004;164(6):1875–82.
45. Lee P, Chandel NS, Simon MC. Cellular adaptation to hypoxia through HIFs and beyond. Nat Rev Mol Cell Biol. 2020;21(5):268–83.
46. Zhuang Y, Liu K, He Q, Gu X, Jiang C, Wu J. Hypoxia signaling in cancer: Implications for therapeutic interventions. MedComm. 2023;4(1):1–37.
47. Castilla DM, Liu Z-J, Velazquez OC. Oxygen: Implications for Wound Healing. Adv Wound Care. 2012;1(6):225–30.
48. Nielson CB, Duethman NC, Howard JM, Moncure M, Wood JG. Burns: Pathophysiology of Systemic Complications and Current Management. J Burn Care Res. 2017;38(1):e469–81.
49. Bhattacharya S, Mishra R. Pressure ulcers: Current understanding and newer modalities of treatment. Indian J Plast Surg. 2015;48(1):4–16.
50. Munteanu C, Teoibaș-Șerban D, Iordache L, Balaurea M, Blendea C-D. Water intake meets the Water from inside the human body – physiological, cultural, and health perspectives - Synthetic and Systematic literature review. Balneo PRM Res J. 2021;12(3):196–209.
51. Burke JF, Yannas O V., Quinby WC, Bondoc CC, Jung WK. Successful use of a physiologically acceptable artificial skin in the treatment of extensive burn injury. Ann Surg. 1981;194(4):413–27.
52. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233–41.

53. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481–8.
54. Severino P, Amato AD, Pucci M, Infusino F, Adamo F, Birtolo LI, et al. Ischemic Heart Disease Pathophysiology Paradigms Overview: From Plaque Activation to Microvascular Dysfunction. From Plaque Act to Microvasc Dysfunction Int J Mol Sci 2020; 21(21)8118 https//doi.org/103390/ijms21218118.
55. Muller MD, Reed AB, Leuenberger UA, Sinoway LI. Physiology in medicine: Peripheral arterial disease. J Appl Physiol. 2013;115(9):1219–26.
56. Mutlak O, Aslam M, Standfield NJ. Chronic venous insufficiency: a new concept to understand pathophysiology at the microvascular level - a pilot study. Perfus (United Kingdom). 2019;34(1):84–9.
57. Scott HJ, Coleridge Smith PD. Tissue oxygenation, venous ulcers and fibrin cuffs. J R Soc Med. 1989;82(10):635–6.
58. Wollina U, Abdel-Naser MB, Mani R. A review of the microcirculation in skin in patients with chronic venous insufficiency: The problem and the evidence available for therapeutic options. Int J Low Extrem Wounds. 2006;5(3):169–80.
59. Kirkham PA, Barnes PJ. Oxidative Stress in Chronic Obstructive Pulmonary Disease. Role Oxidative Stress Chronic Dis. 2014;(x):314–48.
60. Karnati S, Seimetz M, Kleefeldt F, Sonawane A, Madhusudhan T, Bachhuka A, et al. Chronic Obstructive Pulmonary Disease and the Cardiovascular System: Vascular Repair and Regeneration as a Therapeutic Target. Front Cardiovasc Med. 2021;8(April):1–26.
61. Papiris S, Kotanidou A, Malagari K, Roussos C. Clinical review: Severe asthma. Crit Care Febr 2002 Vol 6 No 1, Available online http//ccforum.com/content/6/1/030. 2002;6(1).
62. Yeh SY, Schwartzstein R. Asthma: Pathophysiology and Diagnosis. Asthma, Heal Soc 2009 Jun 8 19–42 Publ online 2009 Jun 8 doi 101007/978-0-387-78285-0_2.
63. Amezcua-Gutiérrez MA, Montoya-Rojo JO, Castañón-González JA, Zamora-Gómez SE, Gorordo-Delsol LA, Hernández-López GD, et al. The maximum expression of hypoxia and hypoventilation: Acute respiratory distress syndrome. Rev Médica del Hosp Gen México. 2018;81(1):47–58.
64. Swenson KE, Swenson ER. Pathophysiology of Acute Respiratory Distress Syndrome and COVID-19 Lung Injury. Crit Care Clin [Internet]. 2021;37(4):749–76. Available from: https://doi.org/10.1016/j.ccc.2021.05.003
65. Böning D, Kuebler WM, Vogel D, Bloch W. The oxygen dissociation curve of blood in COVID-19–An update. Front Med. 2023;10(February):1–15.
66. Hayden SJ, Albert TJ, Watkins TR, Swenson ER. Anemia in critical illness: Insights into etiology, consequences, and management. Am J Respir Crit Care Med. 2012;185(10):1049–57.
67. Li X, Dao M, Lykotrafitis G, Karniadakis GE. Biomechanics and biorheology of red blood cells in sickle cell anemia. J Biomech [Internet]. 2017;50:34–41. Available from: http://dx.doi.org/10.1016/j.jbiomech.2016.11.022
68. Onose G, Anghelescu A, Blendea D, Ciobanu V, Daia C, Firan FC, et al. Cellular and Molecular Targets for Non-Invasive, Non-Pharmacological Therapeutic/Rehabilitative Interventions in Acute Ischemic Stroke. Int J Mol Sci. 2022;23(2):1–36.
69. Fan JL, Nogueira RC, Brassard P, Rickards CA, Page M, Nasr N, et al. Integrative physiological assessment of cerebral hemodynamics and metabolism in acute ischemic stroke. J Cereb Blood Flow Metab. 2022;42(3):454–70.
70. Ferdinand P, Roffe C. Hypoxia after stroke: A review of experimental and clinical evidence. Exp Transl Stroke Med. 2016;8(1):1–8.
71. Mckee AC, Daneshvar DH. The neuropathology of traumatic brain injury [Internet]. 1st ed. Vol. 127, Handbook of Clinical Neurology. Elsevier B.V.; 2015. 45–66 p. Available from: http://dx.doi.org/10.1016/B978-0-444-52892-6.00004-0

72. Muir W. Trauma: Physiology, pathophysiology, and clinical implications. J Vet Emerg Crit Care. 2006;16(4):253–63.
73. Sircan Kucuksayan A, Buyukaksu M, Balci MK, Canpolat M. Investigation of Lower Extremity Tissue Oxygen Saturation in Patients with Diabetes Mellitus. Int J Acad Med Pharm. 2021;Volum: 3,(Volum: 3, Issue: 3):220–3.
74. Ditzel J, Standl E. THE PROBLEM OF TISSUE OXYGENATION IN DIABETES MELLITUS: Its relation to the early functional changes in the microcirculation of diabetic subjects. Acta Med Scand. 1975;197(578 S):49–58.
75. Shock NW, Hastings AB. Studies of the Acid-Base Balance of the Blood. J Biol Chem [Internet]. 1935;112(1):239–62. Available from: http://dx.doi.org/10.1016/S0021-9258(18)74983-1
76. Collins JA, Rudenski A, Gibson J, Howard L, O'Driscoll R. Relating oxygen partial pressure, saturation and content: The haemoglobin–oxygen dissociation curve. Breathe. 2015;11(3):194–201.
77. Curley GF, Laffey JG. Acidosis in the critically ill - balancing risks and benefits to optimize outcome. Crit Care. 2014;18(2):2–4.
78. Jiang L, Shi K, Guo YK, Ren Y, Li ZL, Xia CC, et al. The additive effects of obesity on myocardial microcirculation in diabetic individuals: A cardiac magnetic resonance first-pass perfusion study. Cardiovasc Diabetol [Internet]. 2020;19(1):1–13. Available from: https://doi.org/10.1186/s12933-020-01028-1
79. Clough GF, Kuliga KZ, Chipperfield AJ. Flow motion dynamics of microvascular blood flow and oxygenation: Evidence of adaptive changes in obesity and type 2 diabetes mellitus/insulin resistance. Microcirculation. 2017;24(2).
80. Lempesis IG, van Meijel RLJ, Manolopoulos KN, Goossens GH. Oxygenation of adipose tissue: A human perspective. Acta Physiol. 2020;228(1):1–17.
81. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. Intensive Care Med. 2005;31(10):1316–26.
82. Minasyan H. Oxygen therapy for sepsis and prevention of complications. Acute Crit Care. 2022;37(2):137–50.
83. Singer M, Young PJ, Laffey JG, Asfar P, Taccone FS, Skrifvars MB, et al. Dangers of hyperoxia. Crit Care [Internet]. 2021;25(1):1–15. Available from: https://doi.org/10.1186/s13054-021-03815-y
84. Roy TK, Secomb TW. Effects of impaired microvascular flow regulation on metabolism-perfusion matching and organ function. Microcirculation. 2021;28(3):1–35.
85. Balegar KK V., Jayawardhana M, Martin AJ, de Chazal P, Nanan RKH. Hierarchical improvement of regional tissue oxygenation after packed red blood cell transfusion. PLoS One [Internet]. 2022;17(7 July):1–15. Available from: http://dx.doi.org/10.1371/journal.pone.0271563
86. Luckner G, Dünser MW, Stadlbauer KH, Mayr VD, Jochberger S, Wenzel V, et al. Cutaneous vascular reactivity and flow motion response to vasopressin in advanced vasodilatory shock and severe postoperative multiple organ dysfunction syndrome. Crit Care. 2006;10(2):1–7.
87. Rothhammer A. Gewebsoxygenierung: Physiologische und patho-physiologische aspekte in der intensivmedizin. Anasthesiol Intensivmed Notfallmedizin Schmerztherapie, Suppl. 1998;33(2).
88. Molnar Z, Nemeth M. Monitoring of tissue oxygenation: An everyday clinical challenge. Front Med. 2017;4(JAN):1–6.
89. Lund N, Bengtsson A, Thorborg P. Muscle tissue oxygen pressure in primary fibromyalgia. Scand J Rheumatol. 1986;15(2):165–73.
90. O'Driscoll BR, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. Thorax. 2008;63(SUPPL. 6).
91. Yáñez-Sepúlveda R, Verdugo-Marchese H, Duclos-Bastías D, Tuesta M, Alvear-Ordenes I. Effects of Inspiratory Muscle Training on Muscle Oxygenation during Vascular Occlusion Testing in Trained Healthy Adult Males. Int J Environ Res Public Health. 2022;19(24).

92. Radak Z, Zhao Z, Koltai E, Ohno H, Atalay M. Oxygen consumption and usage during physical exercise: The balance between oxidative stress and ROS-dependent adaptive signaling. Antioxidants Redox Signal. 2013;18(10):1208–46.
93. Almassmoum SM, Balahmar EA, Almutairi ST, Albuainain G, Ahmad R, Naqvi AA. Current clinical status of hydrotherapy; an evidence based retrospective six-years (2012-2017) systemic review. Bali Med J. 2018;7(3):578–86.
94. Becker BE. Aquatic Therapy: Scientific Foundations and Clinical Rehabilitation Applications. PM R [Internet]. 2009;1(9):859–72. Available from: http://dx.doi.org/10.1016/j.pmrj.2009.05.017
95. Bastos CM, Rocha F, Gomes N, Marinho-Reis P. The Challenge in Combining Pelotherapy and Electrotherapy (Iontophoresis) in One Single Therapeutic Modality. Appl Sci. 2022;12(3).
96. Mennuni G, Fontana M, Perricone C, Nocchi S, Rosso R, Ceccarelli F, et al. A meta-analysis of the effectiveness of mud-bath therapy on knee osteoarthritis. Clin Ter. 2021;172(4):372–87.
97. Zafonte RD, Wang L, Arbelaez CA, Dennison R, Teng YD. Medical Gas Therapy for Tissue, Organ, and CNS Protection: A Systematic Review of Effects, Mechanisms, and Challenges. Adv Sci. 2022;9(13).
98. Gottlieb J, Capetian P, Hamsen U, Janssens U, Karagiannidis C, Kluge S, et al. Oxygen Therapy in the Acute Treatment of Adult Patients. AWMF Online [Internet]. 2021; Available from: https://www.awmf.org/fileadmin/user_upload/Leitlinien/020_D_Ges_fuer_Pneumologie/020-021le_S3_Oxygen-Therapy-in-the-Acute-Treatment-of-Adult-Patients_2021-11.pdf
99. Sjöberg F, Singer M. The medical use of oxygen: A time for critical reappraisal. J Intern Med. 2013;274(6):505–28.
100. Nasrullah A, Virk S, Shah A, Jacobs M, Hamza A, Sheikh AB, et al. Acute Respiratory Distress Syndrome and the Use of Inhaled Pulmonary Vasodilators in the COVID-19 Era: A Narrative Review. Life. 2022;12(11).
101. McCartney R, Saha S, Rees J, Lawy T, Mosaheb R. Inhaled nitric oxide: A review of the action, current literature, and an analysis of its use in the NHS today 1A02 2C04. J Intensive Care Soc. 2013;14(3):231–4.
102. Iotti GA, Olivei MC, Palo A, Galbusera C, Veronesi R, Braschi A. Acute effects of inhaled nitric oxide in adult respiratory distress syndrome. Eur Respir J. 1998;12(5):1164–71.
103. Bauer I, Pannen BHJ. Bench-to-bedside review: Carbon monoxide--from mitochondrial poisoning to therapeutic use. Crit Care. 2009;13(4):220.
104. Knauert M, Vangala S, Haslip M, Lee PJ. Therapeutic applications of carbon monoxide. Oxid Med Cell Longev. 2013;2013.
105. Foresti R, Bani-Hani MG, Motterlini R. Use of carbon monoxide as a therapeutic agent: Promises and challenges. Intensive Care Med. 2008;34(4):649–58.
106. Munteanu C, Munteanu D, Onose G. Hydrogen sulfide (H2S) - therapeutic relevance in rehabilitation and balneotherapy Systematic literature review and meta-analysis based on the PRISMA paradig. Balneo PRM Res J. 2021;12(3):176–95.
107. Munteanu C, Rotariu M, Turnea M, Dogaru G, Popescu C, Spînu A, et al. Recent Advances in Molecular Research on Hydrogen Sulfide (H2S) Role in Diabetes Mellitus (DM)—A Systematic Review. Int J Mol Sci 2022 Jun 16;23(12)6720 doi 103390/ijms23126720 PMID 35743160; PMCID PMC9223903.
108. Weerapong P, Hume PA, Kolt GS. The mechanisms of massage and effects on performance, muscle recovery and injury prevention. Sport Med. 2005;35(3):235–56.
109. Gasibat Q, Suwehli W. Determining the Benefits of Massage Mechanisms: A Review of Literature. Artic J Rehabil Sci [Internet]. 2017;2(3):58–67. Available from: http://article.sciencepublishinggroup.com/pdf/10.11648.j.rs.20170203.12.pdf%0Ahttps://www.researchgate.net/publication/318929943

110. Sagar SM, Dryden T, Wong RK. Massage therapy for cancer patients: A reciprocal relationship between body and mind. Curr Oncol. 2007;14(2):45–56.
111. Brummitt J. LITERATURE REVIEW THE ROLE OF MASSAGE IN SPORTS PERFORMANCE AND REHABILITATION : cURRENT EVIDENCE AND FUTURE CORRESPONDENCE : Phys Ther. 2008;3(1):7–21.
112. Vaccarezza M, Vitale M. Crenotherapy: A neglected resource for human health now re-emerging on sound scientific concepts. Int J Biometeorol. 2010;54(5):491–3.
113. Albertini MC, Dachà M, Teodori L, Conti ME. Drinking mineral waters: Biochemical effects and health implications - The state-of-the-art. Int J Environ Heal. 2007;1(1):153–69.
114. Kurowska A, Ziemichód W, Herbet M, Piątkowska-Chmiel I. The Role of Diet as a Modulator of the Inflammatory Process in the Neurological Diseases. Nutrients. 2023;15(6):1436.
115. Fekete M, Szarvas Z, Fazekas-Pongor V, Feher A, Csipo T, Forrai J, et al. Nutrition Strategies Promoting Healthy Aging: From Improvement of Cardiovascular and Brain Health to Prevention of Age-Associated Diseases. Nutrients. 2023;15(1):1–28.
116. Niemelä O, Bloigu A, Bloigu R, Halkola AS, Niemelä M, Aalto M, et al. Impact of Physical Activity on the Characteristics and Metabolic Consequences of Alcohol Consumption: A Cross-Sectional Population-Based Study. Int J Environ Res Public Health. 2022;19(22).
117. Sørensen LT. Wound healing and infection in surgery: The pathophysiological impact of smoking, smoking cessation, and nicotine replacement therapy: A systematic review. Ann Surg. 2012;255(6):1069–79.
118. Sørensen LT, Jørgensen S, Petersen LJ, Hemmingsen U, Bülow J, Loft S, et al. Acute Effects of Nicotine and Smoking on Blood Flow, Tissue Oxygen, and Aerobe Metabolism of the Skin and Subcutis. J Surg Res [Internet]. 2009;152(2):224–30. Available from: http://dx.doi.org/10.1016/j.jss.2008.02.066
119. Singh V, Khatana S, Gupta P, Bhagol A. Supplemental oxygen therapy: Important considerations in oral and maxillofacial surgery. Natl J Maxillofac Surg. 2011;2(1):10.
120. Budinger GRS, Mutlu GM. Balancing the risks and benefits of oxygen therapy in critically ill adults. Chest. 2013;143(4):1151–62.
121. Furian M, Flueck D, Scheiwiller PM, Mueller-Mottet S, Urner LM, Latshang TD, et al. Nocturnal cerebral tissue oxygenation in lowlanders with chronic obstructive pulmonary disease travelling to an altitude of 2,590 m: Data from a randomised trial. J Sleep Res. 2021;30(6):1–9.
122. Marinova R, Groudeva V, Krastev P. Tissue Oxygenation Measurement in Patients With Sepsis Compared To the Lactate Levels and Hemodynamical Monitoring. Comptes Rendus L'Academie Bulg des Sci. 2022;75(8):1202–9.
123. Lin CK, Leu SW, Tsai YH, Zhou SK, Lin CM, Huang SY, et al. Increased tissue water in patients with severe sepsis affects tissue oxygenation measured by near-infrared spectroscopy: a prospective, observational case-control study. Quant Imaging Med Surg. 2022;12(10):4953–67.
124. Acharya D, Mukherjea A, Cao J, Ruesch A, Schmitt S, Yang J, et al. Non-Invasive Spectroscopy for Measuring Cerebral Tissue Oxygenation and Metabolism as a Function of Cerebral Perfusion Pressure. Metabolites. 2022;12(7).
125. Barriteau CM, Chiu A, Rodeghier M, Liem RI. Cerebral and skeletal muscle tissue oxygenation during exercise challenge in children and young adults with sickle cell anaemia. Br J Haematol. 2022;196(1):179–82.
126. Guo F, Jia S, Wang Q, Liu Q, Hu M, Wang W, et al. Which Predictor, SctO2 or SstO2, Is more Sensitive for Postoperative Cognitive Dysfunction in Spine Surgery: A Prospective Observational Study? Orthop Surg. 2023;15(1):276–85.
127. Hashem M, Wu Y, Dunn JF. Quantification of cytochrome c oxidase and tissue oxygenation using CW-NIRS in

a mouse cerebral cortex. Biomed Opt Express. 2021;12(12):7632.

128. Mah AJ, Nguyen T, Ghazi Zadeh L, Shadgan A, Khaksari K, Nourizadeh M, et al. Optical Monitoring of Breathing Patterns and Tissue Oxygenation: A Potential Application in COVID-19 Screening and Monitoring. Sensors. 2022;22(19).
129. Tsukuda J, Fujitani S, Rahman M, Morisawa K, Kawaguchi T, Taira Y. Monitoring tissue oxygenation index using near-infrared spectroscopy during pre-hospital resuscitation among out-of-hospital cardiac arrest patients: a pilot study. Scand J Trauma Resusc Emerg Med. 2021;29(1):42.
130. Sudakou A, Lange F, Isler H, Lanka P, Wojtkiewicz S, Sawosz P, et al. Time-domain NIRS system based on supercontinuum light source and multi-wavelength detection: validation for tissue oxygenation studies. Biomed Opt Express. 2021;12(10):6629.
131. Chauvin J, Akhbardeh A, Brunnemer R, Vasefi F, Bearman G, Huong A, et al. Simulated Annealing-Based Wavelength Selection for Robust Tissue Oxygenation Estimation Powered by the Extended Modified Lambert–Beer Law. Appl Sci. 2022;12(17).
132. Kleiss SF, Ma KF, El Moumni M, Schuurmann RCL, Zeebregts CJ, Haalboom M, et al. Reliability assessment of hyperspectral imaging with the HyperView™ system for lower extremity superficial tissue oxygenation in young healthy volunteers. J Clin Monit Comput [Internet]. 2022;36(3):713–23. Available from: https://doi.org/10.1007/s10877-021-00698-w
133. Chen F, Yan H, Yang F, Cheng L, Zhang S, Li S, et al. Evaluation of renal tissue oxygenation using blood oxygen level-dependent magnetic resonance imaging in chronic kidney disease. Kidney Blood Press Res. 2021;46(4):441–51.
134. Komisarow JM, Toro C, Curley J, Mills B, Cho C, Simo GM, et al. Utilization of Brain Tissue Oxygenation Monitoring and Association with Mortality Following Severe Traumatic Brain Injury. Neurocrit Care. 2022;36(2):350–6.
135. Sargut TA, Vajkoczy P, Wolf S. Adjustable and Magnetic Resonance Imaging Conditional Implantation of a Licox Brain Tissue Oxygenation Probe in Neurosurgery: Technical Note. World Neurosurg [Internet]. 2022;166:29–32. Available from: https://doi.org/10.1016/j.wneu.2022.06.152
136. Kazachkina N, Lymar J, Shcheslavskiy V, Savitsky A. A pilot study of the dynamics of tissue oxygenation in vivo using time-resolved phosphorescence imaging. J Innov Opt Health Sci. 2021;14(5):1–10.
137. Schiavo F, Kjellsson Lindblom E, Toma-Dasu I. Towards the virtual tumor for optimizing radiotherapy treatments of hypoxic tumors: A novel model of heterogeneous tissue vasculature and oxygenation. J Theor Biol [Internet]. 2022;547:111175. Available from: https://doi.org/10.1016/j.jtbi.2022.111175
138. Sonmezoglu S, Fineman JR, Maltepe E, Maharbiz MM. Monitoring deep-tissue oxygenation with a millimeter-scale ultrasonic implant. Nat Biotechnol [Internet]. 2021;39(7):855–64. Available from: http://dx.doi.org/10.1038/s41587-021-00866-y
139. Tseng S-H, Liang B-J, Wang W, Tsai B-X, Hu P-S. Monitoring adaptation of skin tissue oxygenation during cycling ergometer exercise by frequency-domain diffuse optical spectroscopy. Biomed Opt Express. 2021;12(8):5023.
140. Khoo J, Hagemeyer CE, Henstridge DC, Kumble S, Wang TY, Xu R, et al. Effects of water stably-enriched with oxygen as a novel method of tissue oxygenation on mitochondrial function, and as adjuvant therapy for type 2 diabetes in a randomized placebo-controlled trial. PLoS One [Internet]. 2021;16(7 July):1–15. Available from: http://dx.doi.org/10.1371/journal.pone.0254619
141. Bernholm KF, Meyhoff CS, Bickler P. Association between tissue oxygenation and myocardial injury in patients undergoing major spine surgery: A prospective cohort study. BMJ Open. 2021;11(9).

142. Dietrich M, Antonovici A, Hölle T, Nusshag C, Kapp AC, Studier-Fischer A, et al. Microcirculatory tissue oxygenation correlates with kidney function after transcatheter aortic valve implantation–Results from a prospective observational study. Front Cardiovasc Med. 2023;10(February).
143. Bragin DE, Bragina OA, Berliba L, Kameneva M V., Nemoto EM. Addition of Drag-Reducing Polymers to Colloid Resuscitation Fluid Enhances Cerebral Microcirculation and Tissue Oxygenation After Traumatic Brain Injury Complicated by Hemorrhagic Shock. Adv Exp Med Biol. 2021;1269:283–8.
144. John L, Kota AA, Samuel V, Premkumar P, Selvaraj D, Stephen E, et al. Transcutaneous partial pressure of oxygen measurement in advanced chronic venous insufficiency as a marker of tissue oxygenation. Vasc Spec Int. 2021;37:1–6.
145. Kaile K, Mahadevan J, Leiva K, Khandavilli D, Narayanan S, Muthukrishnan V, et al. Tissue Oxygenation Measurements to Aid Scalpel Debridement Removal in Patients With Diabetes. J Diabetes Sci Technol. 2022;16(2):460–9.
146. Robledo EA, Murillo J, Martin RV, Leiva K, Beiner C, Rodrigues MA, et al. Assessment of Tissue Oxygenation and Radiation Dermatitis Pre-, During, and Post-Radiation Therapy in Breast Cancer Patients. Front Oncol. 2022;12(July):1–11.
147. Kharraziha I, Torabi P, Johansson M, Sutton R, Fedorowski A, Hamrefors V. The Influence of Age on Cerebral Tissue Oxygenation in Vasovagal Syncope and Orthostatic Hypotension. J Clin Med. 2022;11(15).
148. AL-Timimi Z. Improvement of antibiotics absorption and regulation of tissue oxygenation through blood laser irradiation. Heliyon [Internet]. 2021;7(4):e06863. Available from: https://doi.org/10.1016/j.heliyon.2021.e06863
149. Wang B, Zhou L, Guo Y, Guo H, Zhong Y, Huang X, et al. Cyanobacteria-based self-oxygenated photodynamic therapy for anaerobic infection treatment and tissue repair. Bioact Mater [Internet]. 2022;12(July 2021):314–26. Available from: https://doi.org/10.1016/j.bioactmat.2021.10.032
150. Schmidt A, Liebelt G, Nießner F, von Woedtke T, Bekeschus S. Gas plasma-spurred wound healing is accompanied by regulation of focal adhesion, matrix remodeling, and tissue oxygenation. Redox Biol. 2021;38(November 2020).
151. Barrit S, Al Barajraji M, El Hadweh S, Dewitte O, Torcida N, Andre J, et al. Brain Tissue Oxygenation-Guided Therapy and Outcome in Traumatic Brain Injury: A Single-Center Matched Cohort Study. Brain Sci. 2022;12(7).
152. Maharjan S, Alva J, Cámara C, Rubio AG, Hernández D, Delavaux C, et al. Symbiotic Photosynthetic Oxygenation within 3D-Bioprinted Vascularized Tissues. Matter. 2021;4(1):217–40.
153. Kajtez J, Wesseler MF, Birtele M, Khorasgani FR, Rylander Ottosson D, Heiskanen A, et al. Embedded 3D Printing in Self-Healing Annealable Composites for Precise Patterning of Functionally Mature Human Neural Constructs. Adv Sci. 2022;9(25):1–13.
154. Dietrich M, Özdemir B, Gruneberg D, Petersen C, Studier-Fischer A, von der Forst M, et al. Hyperspectral imaging for the evaluation of microcirculatory tissue oxygenation and perfusion quality in haemorrhagic shock: A porcine study. Biomedicines. 2021;9(12):1–14.
155. Fan JL, Wu TY, Lovering AT, Nan L, Bang WL, Kayser B. Differential Brain and Muscle Tissue Oxygenation Responses to Exercise in Tibetans Compared to Han Chinese. Front Physiol. 2021;12(February):1–15.
156. Guan S, Lin N, Yin Y, Liu H, Liu L, Qi L. Electromyography Activity , and Tissue Oxygenation during Plyometric Training. Sensors (Basel, Switzerland),. 2021;21(9):3015.
157. Horiuchi M, Okazaki K, Asano K, Friend AT, Rossetti GMK, Oliver SJ. The influence of short-term high-altitude acclimatization on cerebral and leg tissue oxygenation post-orthostasis. Eur J Appl Physiol. 2021;121(11):3095–102.
158. Yamamoto N, Takada R, Maeda T, Yoshii T, Okawa A, Yagishita K. Microcirculation and tissue oxygenation in

the head and limbs during hyperbaric oxygen treatment. Diving Hyperb Med. 2021;51(4):338–44.

159. Samanta D, Prabhakar NR, Semenza GL. Systems biology of oxygen homeostasis. Wiley Interdiscip Rev Syst Biol Med. 2017;9(4).
160. Rivers RJ, Meininger CJ. The Tissue Response to Hypoxia: How Therapeutic Carbon Dioxide Moves the Response toward Homeostasis and Away from Instability. Int J Mol Sci. 2023;24(6):5181.
161. Pittman RN. Oxygen Transport in the Microcirculation and Its Regulation. Microcirculation. 2013;20(2):117–37.
162. Swartz HM, Flood AB, Schaner PE, Halpern H, Williams BB, Pogue BW, et al. How best to interpret measures of levels of oxygen in tissues to make them effective clinical tools for care of patients with cancer and other oxygen-dependent pathologies. Physiol Rep. 2020;8(15):1–20.
163. Perrey S. Muscle Oxygenation Unlocks the Secrets of Physiological Responses to Exercise: Time to Exploit it in the Training Monitoring. Front Sport Act Living. 2022;4(March):1–4.
164. Pittman RN. Oxygen gradients in the microcirculation. Acta Physiol (Oxf). 2011;202(3):311–22.
165. Roussakis E, Li Z, Nichols AJ, Evans CL. Oxygen-Sensing Methods in Biomedicine from the Macroscale to the Microscale. Angew Chemie - Int Ed. 2015;54(29):8340–62.