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Review article

The importance of recognizing the harmful effects of hyperoxia in the treatment of cardiac patients

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Abstract Non-selective use of oxygen therapy can lead to the development of hyperoxia, which is known to cause harmful consequences on multiple organ systems through various mechanisms. Besides its detrimental effects on pulmonary parenchyma, the cardiovascular system represents another target where the detrimental effects of hyperoxia manifest. The pathogenetic mechanism of hyperoxia is based on reducing the bioavailability of NO, increasing systemic vascular resistance, inducing vasoconstriction, reducing oxygen supply to tissues, and inducing additional cellular mechanisms that lead to apoptosis of myocardial cells, decreased stroke volume, and cardiac output. These pathogenetic changes can worsen the clinical condition, especially in patients with myocardial infarction and heart failure. Clinicians need to pay attention to optimal oxygen therapy in specific indications and appropriate dosing (dosage), and highlight the potential harmful effects of hyperoxia that can significantly affect the clinical course of patients.

Key words hyperoxia, cardiovascular diseases

In clinical practice, oxygen therapy is often used non-selectively in patients with myocardial infarctions, heart failure, and other acute cardiac conditions. Oxygen is frequently administered in doses higher than necessary, which not only fails to improve the clinical condition but can also have negative consequences under certain conditions. Despite the knowledge of the harmful effects of oxygen dating back to the 1960s and well-documented recent literature on the adverse effects of hyperoxia in all categories of patients, including those treated on an outpatient basis, in the prehospital and hospital phases, as well as during rehabilitation, there persists an inertia in applying outdated oxygen therapy regimens. [1-8]

To highlight to clinicians the pathogenetic mechanisms underlying the development of harmful effects and clinical manifestations of hyperoxia.

Hyperoxia refers to a condition of elevated oxygen supply to tissues and organs, whereas the toxic effects of oxygen manifest when the partial pressure of alveolar oxygen exceeds that inspired under normal conditions. With continuous exposure to supraphysiological concentrations of oxygen, a state of hyperoxia develops.[6] Based on arterial blood gas analysis, hyperoxia is defined as a finding of partial pressure of oxygen (PaO_2) greater than 100 mmHg to 125 mmHg (13.3- 16.7kPa) depending on the literature.[3]

Hyperoxia exhibits adverse effects on the entire organism, and the adverse effects on the cardiovascular system can be evaluated only as part of the mutual and additive multi-organ action. Table 1 illustrates the pathophysiological mechanisms of hyperoxia on the major organ systems. [2-6]

The negative effects of hyperoxia on hemodynamics and the cardiovascular system as a whole occur via two key systemic effects, including direct vasoconstriction and the generation of toxic reactive oxygen species (ROS).[4] Supraoptimal oxygen level used with the aim of improving tissue oxygenation in hypoxic patients, paradoxically leads to the opposite effect, resulting in reduced oxygen release to tissues. The main mechanism by which hyperoxia leads to this phenomenon is based on vasoconstriction. This leads to increased systemic vascular resistance and decreased blood flow by 10-30% in the coronary, cerebral, and vascular systems.[2] It is logical that the reduction in oxygen release to tissues leads to an increase in the ischemic zone in acute myocardial infarction, and it may lead to arrhythmias, recurrent myocardial infarction, and negative cardiac remodeling.[3] The mechanism via the negative effects of reactive oxygen species (ROS), mitochondrial stress, leads to cellular apoptosis and myocardial cell death. It is also important to consider the role of hyperoxia in activating the parasympathetic nervous system and the onset of bradycardia, which further has significant implications for clinical management and drug administration.[6] The reduction in the bioavailability of nitric oxide (NO) induced by hyperoxia affects the onset of endothelial dysfunction,

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Table 1. Pathophysiology mechanisms of the occurrence of adverse effects of hyperoxia[3-6]

PATHOPHYSIOLOGY MECHANISMS OF THE OCCURENCE OF ADVERSE EFFECTS OF HYPEROXIA	
Cardiovascular system	• ↓ cardiac output and stroke volume • ↑ systemic vascular resistance • ↓ NO bioavailability • ↓ heart rate
Respiratory system	• Lung inflammatic edema • Hyperoxic acute lung injury • Bronchopulmonary dysplasia • Absorption atelectasis • ARDS • COPD; • Hypercapnia
Central nervous system	• Direct neurotoxicity • Reduced myelination • Activation of parasympathetic nervous system • *Paul Bert effect (toxic CNS effects)*
Renal function	• Reduced renal blood flow • Tubular necrosis • Glomerular dysgenesis • Acute kidney injury
Cellular level	• Reactive oxygen species • Mitochondrial stress • Cellular injury • Apoptosis • Cell death • Pro-inflammatory signaling (NF-kB, IL-6, TGF-B, ET-1) (Lipid peroxidation, sulfhydryl protein oxidation, DNA damage, reduction of cellular reducing agents)

which represents the fundamental pathogenetic mechanism of the development and acceleration of atherosclerosis, the primary cause of coronary artery disease.[3-6]

It has been found that the earlier routine use of oxygen therapy in patients with acute myocardial infarction is not only not beneficial in normoxemic patients but can also lead to harmful effects.[5-8]

The AVOID study (*Australian Air Versus Oxygen in Myocardial Infarction*) randomized 441 patients with STEMI type of myocardial infarction, registering larger infarct areas on magnetic resonance imaging, increased cardiac biomarkers, and a higher incidence of recurrent myocardial infarctions in patients who used oxygen therapy at 8 L/min via nasal mask compared to those who did not receive oxygen therapy. In contrast, the SOCCER study (*Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion*), which randomized 100 normoxemic STEMI patients prescribed oxygen therapy at 10 L/min and those on room air, did not find a statistically significant difference in the size of the infarct zone or the myocardial salvage index examined with CMR (Cardiac magnetic resonance).[2] The DETO2X-AMI randomized study of 6629 patients during the administration of 6 L/min over 6-12 hours did not reveal a change in overall mortality, hospitalization due to heart failure, or cardiovascular death within one year.[2]

According to the latest recommendations of the European Society of Cardiology, oxygen therapy is justified in patients with acute myocardial infarction if oxygen saturation is below 90% (Class I). Otherwise, in patients who are not significantly hypoxic (SaO2 >90%), oxygen therapy is not recommended and may be considered harmful (Class III).[9]

Hyperoxia in patients with heart failure also leads through the mechanism of vasoconstriction to an increase in afterload, systemic vascular resistance, and thereby a decrease in stroke volume and cardiac output.[6,10,11] It is important to emphasize the additional effect of hyperoxia on reducing oxygen distribution to tissues and consequent cellular changes. Routine oxygen therapy is not recommended in patients with acute heart failure. Hyperoxygenation can disrupt the matching of ventilation and perfusion and thereby suppress ventilation, leading to hypercapnia. Therefore, in this patient group, caution should be exercised with the use of oxygen therapy, with monitoring of acid-base balance, SaO2, and SaCO2.[9,10,11] The ELSO registry (*Extracorporeal Life Support Organization*) found that patients with hyperoxemia, defined as PaO2 > 100mmHg within 24 hours after initiation, have a higher degree of in-hospital mortality.[2]

Conclusion

In clinical practice, attention should be paid to the rational use of oxygen therapy, which undoubtedly has a beneficial effect in therapy, especially in those with SaO2 below 90%. However, it must be kept in mind that the use of oxygen in unjustified indications or in excessive doses in justified indications can cause more harmful effects and worsen the prognosis of patients. Additional basic and clinical studies are expected to determine the precise detection of hyperoxia within a time-limited interval and highlight its significance in everyday practice.

Table 2. Summary effect size of acute hyperoxia-induced changes of different clinical state[4]

Summary effect size of acute hyperoxia-induced changes of different clinical state						
	Heart rate	Stroke volume	Cardiac output	Mean arterial pressure	Systemic vascular resistance	Oxygen delivery
Healthy volonteers	↓↓	↓	↓↓	NS	↑↑	NS
Coronary artery disease	↓	NS	↓↓	↑	↑↑	-
Heart failure	NS	↓↓	↓↓	NS	↑↑↑	-
CABG	↓	-	NS	NS	↑↑	-
Sepsis	NS	-	NS	NS	NS	NS

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Sažetak

Značaj prepoznavanja štetnih efekata hiperoksije u lečenju kardioloških bolesnika

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Neselektivna primena oksigenoterapije može uzrokovati nastatanak hiperoksije za koju je poznato da preko brojnih mehanizama uzrokuje štetne posledice na više organskih sistema. Pored štetnog dejstva na plućni parenhim, kardiovaskularni sistem predstavlja drugo ciljno mesto na kome se ispoljavaju detrimentalni efekti hiperoksije.
Patogenetski mehanizam hiperoksije zasniva se na smanjenju bioraspoloživosti NO, povećanju sistemske vaskularne rezistencije, nastanku vazokonstrikcije, redukciji snadbevanja kiseonika tkivima i indukovanju dodatnih celularnih mehanizama koji dovode do apoptoze ćelija, smanjenja udarnog i minutnog volumena srca. Navedene patogenetske promene mogu uzrokovati pogoršanje kliničkog stanja, naročito kod bolesnika sa infarktom miokarda i srčanom insuficijencijom.
Kliničarima je potrebno skrenuti pažnju na optimalizaciju terapije kiseonikom u određenim indikacijama i adekvatnoj dozi i ukazati na potencijalne štetne efekte hiperoksije koji mogu značajno uticati na klinički tok bolesnika.

Ključne reči: *hiperoksija, kardiovaskularne bolesti*