The determinants for oxygen delivery: is increased fraction of inspired oxygen always crucial?

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Abstract

Oxygen (O_2) therapy consists in the administration of a gas mixture with a percentage of O_2 increased and it is one of the most common aids used in hypoxia. In this paper we presented the data analyzed by Huang, as a pretext to try to provide an explanation of the physiopathological effects of oxygen administration on tissue oxygenation. The rationale of O_2 therapy is to increase the inspired partial pressure of O_2, increasing the fraction of inspiratory O_2. Oxygen induces a vasoconstriction on sistemic circulation and this effect reduces the cardiac output, increasing the afterload. The mechanisms by which hyperoxia induces vasoconstriction are different. Oxygen also has effects on lung function, redox balance, and it is involved in the production of reactive O_2 species (ROS) and other systemic effects, which in turn are involved in the changes of reduced oxygen delivery (DO_2). This last would possibly help to consider carefully the risk of DO_2 in each patient.

Introduction

In aerobic organisms, energy is produced by the oxidative metabolism of nutrients, a process in which oxygen (O_2) is consumed.[1]

Respiratory failure is the inadequacy of the respiratory system to perform gas exchange, which involves the inability to ensure physiological oxygenation compared to the tissue needs.[2] It is one of the most important reasons for admission in intensive care unit (ICU).[3]

Oxygen therapy consists in the administration of a gas mixture with a percentage of O_2 increased and it is one of the most common aids used in hypoxia.[4] The O_2 can be administered with different tools, with which you can obtain different flows and inspiratory pressures.[5] However, its hemodynamic effects and the consequences on tissue oxygenation are still not entirely clear.[4]

Methods and Results

In this paper we analized the data originally collected from Leach,[6] and subsequently analyzed by Huang,[7] as a pretext to try to provide an explanation of the physiopathological effects of O_2 administration on tissue oxygenation; and to frame in a pathophysiological context the revisions that are involving several guidelines on the administration of O_2.

The data show the relative effect that the changes in fraction of inspired oxygen (FiO_2), partial pressure of oxygen in arterial blood (PaO_2), saturation of oxygen in arterial blood (SaO_2), Hemoglobin (Hb) and cardiac output (CO) have on the oxygen delivery (DO_2). We want to bring attention to the fact that the increase of the fraction of inspiration oxygen (FiO_2) from 21 to 35%, that is by 14 percentage points, is able to increase the DO_2 of 22% (Figure 1). While the increase of FiO_2 from 35 to 60%, that is by 25 percentage points, increases DO_2 by only 9% (Figure 1).

Discussion

The analysis of the parameters of oxygenation allows us to explain this phenomenon. The arterial oxygen content (CO_2) is the sum of the O_2 bound to Hb and the proportion of dissolved O_2 in plasma. The first term is calculated as the product of the concentration of Hb multiplied by the arterial haemoglobin saturation multiplied by the ability of Hb to bind O_2, that, at least in theory, corresponds to the number of Hüfner, that is the volume of O_2 measured in vitro that can be transported from one gram of Hb: 1.39 mL O_2/grHb. The second term follows Henry's law, that says that, at constant temperature, the solubility of a gas is directly proportional to the pressure that the gas exerts on the solution. Then the proportion of dissolved oxygen is calculated by multiplying the partial pressure of O_2 by the solubility coefficient of O_2.[8]

The rationale of oxygen therapy is to increase the inspired partial pressure of O_2, increasing the fraction of inspiratory O_2, according to the Dalton's law of the partial pressures.[8] It says that the total pressure exerted by an mixture of ideal gases, is equal to the sum of the partial pressures of every gases. Increase the fraction of a gas increases its pressure. This allows to increase the partial pressure of alveolar O_2. According to the Fick's laws, this increases the amount of O_2 that diffuses through the alveolar-capillary membrane and increases blood pressure of O_2.[9] Fick's laws are used in the study of the transport of matter through biological membranes. Fick's laws describe the non-linear concentration variations of a substance which diffuses through membranes. the flow of the diffusing species is directly proportional to the concentration gradient of the species (the movement of the current is from a higher concentration to a lower one), to the diffusivity, to the surface of the membrane, and inversely proportional to the membrane thickness. Increasing the alveolar concentration of O_2, a larger proportion of O_2 diffuses through the alveolar-capillary barrier. However, adequate systemic oxygenation requires an adequate O_2 peripheral distribution. Oxygen delivery is the amount of O_2 delivered to the whole body from the lungs.[4] It is the product of cardiac output multipled by the O_2 content of arterial blood. Cardiac output is a flow, so it is governed by the hydraulic analogy of the Ohm's law, according to which the flow of a fluid through a conduit depends on the pressure gradient at the ends of the duct and on the vascular resistance to the flow (due to the resistance to the constant flow and the resistance to the change of the flow).[1] Vasoconstriction increases the resistance to

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flow, and thus reduces the cardiac output.

Oxygen induces a vasoconstriction on sistemic circulation and this effect reduces the cardiac output, increasing the afterload. As determined by Hagen and Poiseuille, vasoconstriction is the hemodynamic factor that has the greatest effect on the flow.[10] Hagen and Poiseuille have determined the main factors that affect the resistance to laminar flow. The mathematical equation that describes their results is:

$$Q=(DP\ p\ r4)/(8\ L\ m) \qquad \text{(eq. 1)}$$

where: Q is the volumetric flow rate; DP is the pressure drop; p is the mathematical constant Pi; r is the radius of the conduct; L is the length of the conduct; and m is the dynamic viscosity. According to their formula, the flow is directly proportional to the fourth power of the radius vascular, which is its main determinant.

Various evidences have been provided that systemic vasoconstriction mediated by O_2 reduces the cardiac output, in particular Thomson *et al.*[11] have shown that the administration of FiO_2 at 85%, increases the systemic vascular resistance index by 18.9±1.9% ($P<0.001$) and reduces the cardiac index by -10.3±1.7% (Figure 2, yellow line). It is also important that these effects persist after the restoration of breathing ambient air for 1 h at least.

These data have been confirmed by other authors, in particular Demchenko *et al.*[12] have demonstrated that the cerebral vasoconstriction is even more accentuated.

In a study of DeGaute,[13] patients with acute exacerbation of chronic obstructive pulmonary disease (COPD) who received O_2 (FiO_2=26%) have had an average DO_2 significantly lower than those who breathed room air. Also Carriveau *et al.*[14] demonstrated that DO_2 may fail to increase in some patients with COPD when supplemental O_2 is administered because of a reduction in cardiac output.

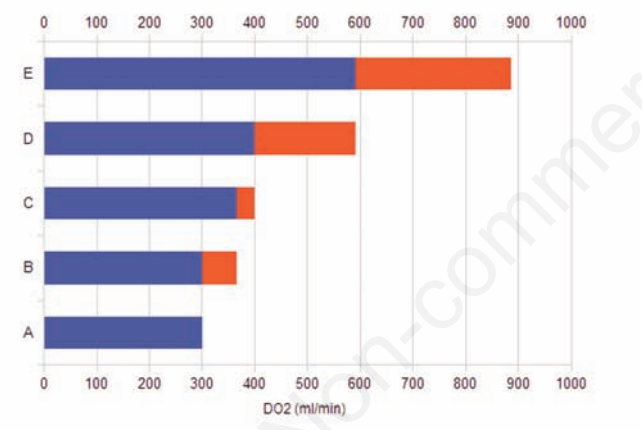
This is consistent with the observation that inhalation of O_2 does not protect against myocardial ischemia.[15]s Also, a coronary vasoconstriction has been demonstrated,[16] which contributes to the reduction of cardiac function.

The mechanisms by which hyperoxia induces vasoconstriction are different. For some of them a clear evidence of a direct connection cause and effect has been given. In particular, hyperoxia: i) evokes -adrenergic stimulation;[17] ii) induces the production of ROS[18] (which will be discussed later, because they have other systemic effects); iii) blocks the cyclooxygenase, with a decreasing production of vasodilator prostaglandins;[19] iv) blocks nitric oxide synthase (NOS) and reduces nitric oxide (NO) [O_2 free radicals (ROS) have inhibitory effects on NOS, they block the catabolism of DMetil-arginine asymmetric, antagonist of L-arginine, and they directly react with NO, producing peroxynitrite and reducing its bioavailability];[19] v) increases production of endothelin (ET-1);[20] and vi) activates the renin-angiotensin system (RAS) inducing Ang II type 1 receptor (AT1R) expression.[21]

In addition, O_2 also has many other effects that in turn have effects on oxygenation.

In a study conducted in UK, the 34% of the patients with a riacutization of COPD has showed evidence of hypercapnia induced by O_2 therapy.[22] The O_2, in fact, also acts on lung function. In chronic hypercapnic patients, a correction of hypoxia relative with O_2 flows too high eliminates the hypoxic stimulus to the respiratory drive, leading to a consequent hypoventilation.[23]

Moreover, increasing the percentage O_2 in the alveolar air causes an absorption of a greater alveolar air share. Then the radius alveolar, at the end of inspiration, is smaller. This increases the transalveolar pressure, that, according to the law of Laplace, is directly proportional to the radius, and promotes atelectasis. It has been shown that inhalation of FiO_2 equal to or greater than 0.60 reduces the vital capacity.[24] At the level of pulmonary circulation, the O_2 causes vasodilation.[8] While



FiO2 (%)	PaO2 (kPa)	SaO2 (%)	Hb (gr/dl)	CO (L/min)	
60	16,5	98	10,5	6	E
60	16,5	98	10,5	4	D
60	16,5	98	7	4	C
35	9	92	7	4	B
21	6	75	7	4	A

Figure 1. Relative effect that the changes in FiO_2, PaO2, SaO_2, Hb and CO have on DO_2 shown as changes to the DO_2 made by increasing the individual determniants for subsequent steps. The blue bars show the value of DO_2 of the preceding step. The red bars show the effect of sequential interventions on DO_2 determinants. Values of the main determinants of DO_2 for each step are also shown.

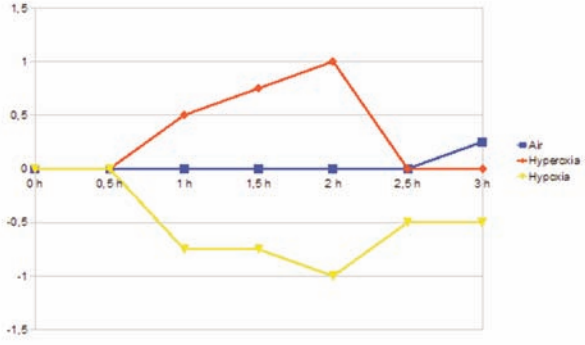


Figure 2. Measurements of the hemodynamic effects that produce the variations of FiO_2. Hypoxia (red line) produces a rise in cardiac index, while the hyperoxia (yellow line) produces a reduction in cardiac index that persisted after the restoration of breathing ambient air (blue line) for 1 h at least.

this can be beneficial for patients with COPD, who have pulmonary hypertension,[25] on the other hand it can alter hypoxic pulmonary vasoconstriction, alter the balance between ventilation and perfusion and so favor the establishment of a shunt effect.[8]

At systemic level, O_2 activates the fibroblasts and the neoangiogenesis,[26] however, it reduces the action of pyruvate dehydrogenase,[27] slowing the Krebs cycle.

Oxygen also alters the function of ATPase Na/K[27] and experimental evidences support the involvement of O_2 in the increasing neuronal excitability, which reduces the seizure threshold.[28]

The O_2 is tossic and potentially letal.[18] The molecolar O_2, in fact, has two electrons not paired. In accordance with the Pauli exclusion principle, you cannot add a pair of electrons to O_2 to reduce it to water, with a single reaction, but it requires a succession of single-electron reduction reactions, which produce highly reactive intermediates – the ROS.[18]

These can alter the DNA, the lipids, and the src homology (SH)-containing proteins. They are involved in the inflammation and in the oxidative stress. In normal conditions, there are many mechanisms to maintain homeostasis redox equilibrium, but in a patient with increased oxidative stress, these mechanisms are frequently depleted.[29] In these conditions, depending on the microenvironment, on the depletion of various antioxidant systems, on the availability of reactive oxidant substrates and on the presence of free metal cofactors, the same antioxidant systems acquire prooxidant action due to the conditional prooxidant effect.[30]

In addition, O_2 increases the production of tumor necrosis factor alpha (TNF) and isoprostane and the activation of caspase 3 and 9.[31]

There are clinical observations that show that serious hypoxemia is tolerated without evidence of inadequate tissue oxygenation.[32,33] In a study of patients with exacerbation of COPD with severe hypoxemia (<40 mmHg) there was no evidence of dysoxia, even with levels of PaO_2 equal to 22 mmHg.[34] In patients at rest, even the most severe form of hypoxemia from lung failure in itself does not involve generalized tissue anaerobiosis.[23]

Directions and guidelines

Therefore, O_2 administration is used for many disorders causing hypoxia. However, the tissue O_2 delivery is determinated by an adequate function of cardiovascular, haematological and respiratory systems. So, perhaps it is more scientifically appropriate to use parameters of tissue oxygenation, as well as function parameters of these systems to decide to administer and monitor O_2 administration.

One solution would be to carefully consider the risk of reduced DO_2 in each patient. According to Fink,[4] patients with adequate Hb concentration, rheological properties of the blood and a preserved cardiac output are able to maintain an adequate transport of O_2, even with a saturation of 85%. If the cardiac output is compromised or tissue metabolic demands is increased, it might be cautious to monitor the effects of O_2 on DO_2 and possibly assess the need for ventilatory support.

Conclusions

In light of these considerations it can be understood why different guidelines are progressively reducing the indication to the administration of O_2.[35,36] This is particularly true for diseases in which a rise of cardiac work or oxidative stress are able to worsen the prognosis. In conclusion, despite being so widespread, new studies are needed to determine the effects and define the indications for O_2 therapy.

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