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PHYSIOLOGICAL NOTE

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Hypoxemia due to increased venous admixture: influence of cardiac output on oxygenation

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Introduction

In the hypoxemic patient under mechanical ventilation, changes in cardiac output may influence the level of arterial oxygenation, with several and sometimes opposite effects. The purpose of this Physiological Note is to give the reader the physiological background to understand these effects, which are often highly relevant for the bedside management of patients with acute lung injury.

In the healthy lung, the venous blood returning to the right heart and flowing through the pulmonary artery to the pulmonary capillaries will be fully saturated by oxygen during the passage through the alveolar part of the capillary. The prerequisite for complete saturation of hemoglobin with oxygen is sufficiently high oxygen partial pressure in the alveoli. Complete saturation is approached if the alveolar partial pressure of oxygen exceeds 13.3 kPa (100 mmHg). This prerequisite is achieved during normoventilation of ambient air with normal lungs at the sea level. Hypoventilation (increased alveolar CO_2) and decrease in barometric pressure (increased altitude) both reduce the alveolar PO_2 – an effect which can be readily counteracted by increasing the inspired fraction of oxygen. The degree of hypoxemia in these circumstances can be predicted from the PO_2 of ideal alveolar gas and the oxyhemoglobin dissociation curve.

What does venous admixture measure?

Venous admixture is used to describe situations in which the oxygenation of the arterial blood is less than that expected for the pulmonary end-capillary blood (100%, if the alveolar partial pressure of oxygen exceeds 13.3 kPa). Venous admixture is the *calculated* amount of mixed venous blood needed to bypass the alveoli and mix with the arterial blood to produce the observed degree of arterial hypoxemia. In other words, venous admixture represents the *calculated* fraction of cardiac output completely bypassing oxygenation in the lung if the rest of the cardiac output is fully oxygenated (assumed to be the case in the absence of inspired gas hypoxia) [1]. A pulmonary artery catheter is necessary to obtain true mixed venous blood.

The venous admixture (Qs/Qt) can be calculated as

$$Qs/Qt = (CcO_2 - CaO_2)/(CcO_2 - CvO_2), \quad (1)$$

where CcO_2 is the pulmonary venous capillary oxygen content in the ideal (i.e., normally ventilated and perfused) alveoli, and CaO_2 and CvO_2 are the arterial and mixed venous oxygen content, respectively. For the ideal alveoli, CcO_2 = Hgb (hemoglobin; g/l) × 1.34 + 0.2325 × alveolar PO_2 (kPa), assuming 100% saturation of the pulmonary and capillary blood.

Apart from hypoventilation, increased venous admixture or physiologic intrapulmonary shunt is the most

common cause of hypoxemia in critically ill patients. In this paper, "venous admixture" and "physiologic shunt" are used interchangeably. The term "physiologic shunt" should not be confused with the presence of slight venous admixture in the normal lungs (around or below 5%); the venous admixture in the normal lungs results from venous blood flow through the thebesian veins (cardiac venous effluent directly into the left heart) and the deep true bronchial veins (into the pulmonary veins), and from the presence of a small amount of ventilation/perfusion mismatch.

What causes increased venous admixture?

Venous admixture can be caused by true shunt (blood flow through alveoli that are not ventilated at all, i.e., alveoli with a ventilation/perfusion = 0), and by ventilation/perfusion mismatch (alveoli with a low ventilation/perfusion). For further information on the concept of ventilation/perfusion matching see the Physiological Note by Calzia and Radermacher [2]. In the non-ventilated alveoli, oxygen will be transported to the capillary blood until the alveolar PO_2 approaches the mixed venous PO_2. In the alveoli with low ventilation/perfusion, the amount of oxygen reaching the alveoli per unit of time is smaller than the amount needed to fully saturate the venous blood arriving at the alveolar capillary per unit of time. Hence, the alveolar PO_2 will decrease until the amount of oxygen reaching the alveoli through ventilation equals the amount transferred to the blood flowing through the alveoli (blood flow × arteriovenous oxygen content difference); the consequence of the low ventilation/perfusion is that only partly oxygenated blood will be mixed in the pulmonary venous blood. The calculation of venous admixture assumes that the mixed venous blood is either fully oxygenated or not oxygenated at all – hence, it cannot differentiate between true shunt and low ventilation/perfusion [3, 4]. It should be noted that hypoxemia due to diffusion problems also causes an increase in the calculated venous admixture, although no shunt or ventilation/perfusion mismatch would be present.

Venous admixture and interaction between mixed venous and arterial oxygenation

In the healthy lungs, arterial oxygenation is defined almost completely by the alveolar oxygen partial pressure. When venous admixture increases, mixed venous oxygenation will have a progressively larger impact on arterial oxygenation. This interaction can be interpreted using the Fick equation (Eq. 2) for oxygen consumption (VO_2) together with the equation for venous admixture (Eq. 1). The VO_2 can be calculated as the product of cardiac output (CO) and arterial-mixed venous oxygen content difference:

$$VO_2 = CO \times (CaO_2 - C\bar{v}O_2), \tag{2}$$

This can be rewritten as

$$C\bar{v}O_2 = CaO_2 - VO_2/CO, \tag{3}$$

or as

$$CaO_2 = C\bar{v}O_2 + VO_2/CO. \tag{3'}$$

The equation for venous admixture (Eq. 1) can be rearranged and written as

$$\begin{aligned} CaO_2 = {} & CcO_2 \times (1 - Qs/Qt) \\ & + C\bar{v}O_2 \times Qs/Qt. \end{aligned} \tag{4}$$

Equations 3 and 4 can be combined to

$$\begin{aligned} CaO_2 = {} & CcO_2 - (VO_2/CO) \\ & \times (Qs/Qt)/(1 - Qs/Qt) \end{aligned} \tag{5}$$

and Eqs. 3′ and 4 to

$$\begin{aligned} C\bar{v}O_2 = {} & CcO_2 - (VO_2/CO) \\ & \times [1 + (Qs/Qt)/(1 - Qs/Qt)]. \end{aligned} \tag{6}$$

If the dissolved oxygen is ignored, Eqs. 5 and 6 can be written as

$$\begin{aligned} SaO_2 = {} & 1 - (VO_2/CO \times Hgb \times 1.34) \\ & \times (Qs/Qt)/(1 - Qs/Qt), \end{aligned} \tag{5'}$$

$$\begin{aligned} SvO_2 = {} & 1 - (VO_2/CO \times Hgb \times 1.34) \\ & \times [1 + (Qs/Qt)/(1 - Qs/Qt)]. \end{aligned} \tag{6'}$$

Equations 5′ and 6′ demonstrate that in the presence of increased venous admixture, arterial oxygenation (SaO_2) is directly related to cardiac output and hemoglobin, and inversely related to oxygen consumption. The effect of these variables on arterial oxygenation will be markedly magnified in the presence of large Qs/Qt [5]. These equations can be applied to demonstrate the interactions between venous admixture, arterial and mixed venous oxygenation, cardiac output, hemoglobin and oxygen consumption (Figs. 1, 2).

Cardiac output and increased venous admixture

In the interactions between venous admixture, arterial oxygenation, and mixed venous oxygenation in the clinical setting, cardiac output has the largest variability. As shown in Fig. 1, an infinite number of arterial and mixed venous saturation lines form two concave surfaces, as a function of cardiac output and venous admixture. These surfaces slope progressively downwards when cardiac output decreases and the venous admixture increases. An increase in oxygen consumption and a decrease in

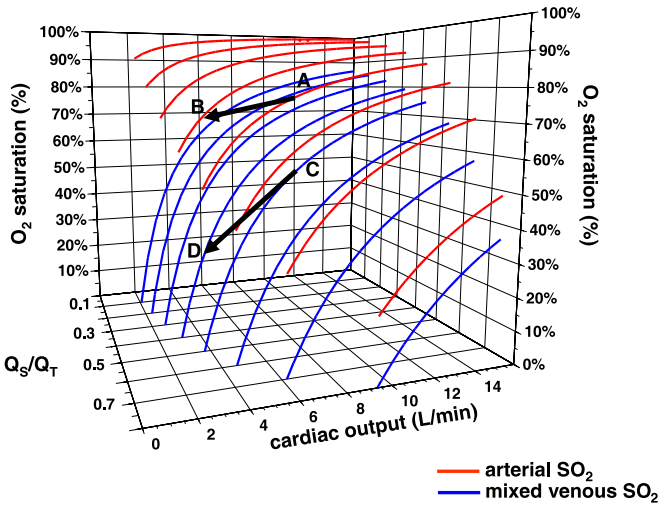

Fig. 1 The relationship between venous admixture (*Qs/Qt*), arterial and mixed venous saturation and cardiac output. For the calculations, dissolved oxygen has been ignored; a hemoglobin of 100 g/l and an oxygen consumption of 250 ml/min have been assumed. Points *A* and *B* represent the effect of cardiac output decreasing from 8 l/min to 4 l/min. The venous admixture is likely to decrease – in this case from 0.50 to 0.40. Since the decrease in cardiac output is accompanied by increased oxygen extraction, the mixed venous saturation decreases substantially (points *C* and *D*), and the net effect is worsened arterial hypoxemia

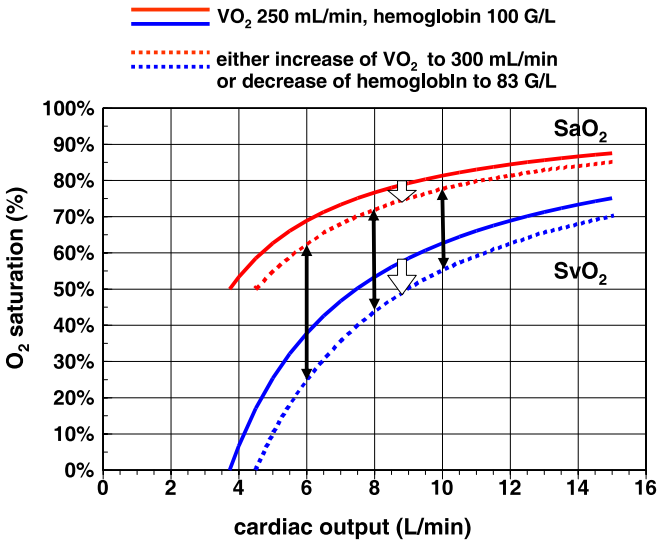

Fig. 2 Effect of oxygen consumption and hemoglobin on arterial (*red*) and mixed venous (*blue*) oxygenation. The *solid curves* are taken from Fig. 1 and represent a physiologic shunt of 50%. A similar proportional increase in oxygen consumption and decrease in hemoglobin have identical effects: in both cases the whole family of arterial (*red dotted line*) and mixed venous (*blue dotted line*) saturation curves shown in Fig. 1 shifts downwards (*open arrows*) and the arterial–venous saturation difference widens (*solid arrows*)

hemoglobin both move the surfaces down and increase the distance between them. This is shown for one pair of saturation lines at 50% physiologic shunt in Fig. 2. In order to maintain a given level of metabolic activity (250 ml/min of VO_2, hemoglobin 100 g/l in Fig. 1), the cardiac output has to increase if the venous admixture increases. Thus a cardiac output of approximately 4 l/min under the conditions shown in Fig. 2 (250 ml/min of VO_2, hemoglobin 100 g/l) would result in mixed venous saturation approaching zero – a situation incompatible with survival. Assuming that a mixed venous saturation of 40–50% could be tolerated in the acutely ill patient over a reasonable period of time, a minimum cardiac output of 6–7.5 l/min would be necessary. A higher metabolic activity or a lower hemoglobin (Fig. 2) would necessitate even higher levels of cardiac output. This example demonstrates the fundamental role of cardiac output in states with acute major increases in physiologic shunt, such as in severe acute respiratory distress syndrome (ARDS).

Acute changes in cardiac output are likely to cause parallel changes in physiologic shunt, which tend to counteract the changes imposed on arterial oxygenation [6, 7]: when cardiac output decreases, the physiologic shunt decreases as well. Decreased cardiac output reduces mixed venous oxygenation, and thereby also arterial oxygenation. Although the physiologic shunt is likely to decrease in parallel with cardiac output, the favorable effect of reduced shunt on arterial oxygenation is at least in part set off by the lower mixed venous oxygenation. Even if the venous admixture were to decrease enough to completely abolish the effect of a concomitant reduction of mixed venous oxygenation on arterial oxygenation, this would result in decrease in oxygen delivery to the tissues in proportion with the decrease in cardiac output. Conversely, if an acute increase in cardiac output increases the physiologic shunt enough to abolish the impact of an increased mixed venous oxygenation on arterial oxygenation, the oxygen delivery to the tissues will increase in proportion with the increase in cardiac output.

If an increase in cardiac output from 6.5 l/min to 9.5 l/min increases venous admixture from 40% to 50% while the hemoglobin and oxygen consumption remain unchanged, the arterial saturation remains unchanged (at around 81% in the example in Fig. 3), but the mixed venous saturation increases from 52% to 61% and the systemic oxygen delivery by 46%. In the clinical setting, the magnitude of individual responses in physiologic shunt to acute changes in cardiac output varies widely, although the directional changes are usually parallel. In contrast to deliberately induced increases in cardiac output, acute spontaneous increases in cardiac output are often accompanied by increased metabolic demand. As discussed before, an increase in oxygen consumption will shift the relationship between arterial and mixed venous saturation towards desaturation of both, and widen the arterio-venous oxygen content difference (Figs. 1, 2),

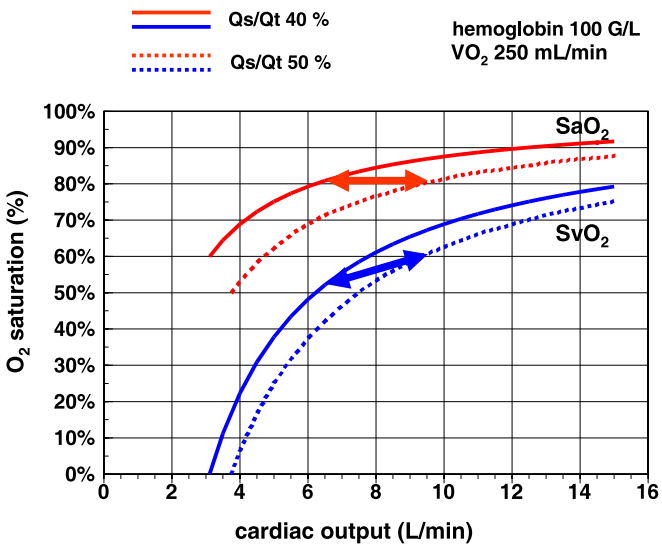

Fig. 3 Effect of an increase in cardiac output from 6.5 to 9.5 l/min and a simultaneous increase in physiologic shunt from 40% to 50% on arterial (*red arrow*) and mixed venous (*blue arrow*) oxygenation. The effect of increased physiologic shunt on arterial oxygenation is completely eliminated due to increased mixed venous saturation, and the whole body oxygen delivery is increased substantially (by 46%)

thereby reducing the positive effect of an increased cardiac output.

The mechanism by which cardiac output and the physiologic shunt change in parallel is not certain; the most likely explanation is that changes in mixed venous oxygenation alter the hypoxic pulmonary vasoconstriction [8]. This would also explain the intra- and interindividual variability in the changes in physiologic shunt in response to changes in cardiac output observed in the clinical setting: changes in local and circulating endo- and exogenous vasoactive substances in sepsis, acute lung injury/ARDS and shock may modify the hypoxic pulmonary vasoconstriction.

Implications for treatment of acute hypoxemia

Diverse pathologies increase the venous admixture, e.g., atelectasis, pulmonary edema of any etiology, and infections and inflammatory processes that reduce the ventilation/perfusion locally or regionally in the lung. The treatment strategy should aim at prompt correction of the cause. While this may be possible in atelectasis, in most other conditions prolonged support of oxygenation is likely to be necessary. Since atelectatic components are common in many situations in which hypoxemia is due to increased venous admixture, maneuvers to re-expand the atelectatic lung regions and to keep them open (recruitment, positive airway pressure, prone positioning) should be considered. When hypoxemia and increased physiologic shunt persist despite these maneuvers, it is advisable to consider the interaction of arterial and mixed venous oxygenation in the management of the hypoxemia. Typical therapeutic measures (increased positive end-expiratory and mean airway pressure) are likely to reduce cardiac output and mixed venous oxygenation. Hence, the cost of attempts to improve or maintain arterial oxygenation may be reduced oxygen delivery to the tissues. On the other hand, increased cardiac output, even if accompanied by increased venous admixture, may result in well-maintained arterial oxygenation and increased oxygen delivery. In addition, reducing oxygen consumption and increasing hemoglobin should be considered (Fig. 2). All these measures to increase mixed venous oxygenation may be worthwhile, especially in patients with low mixed venous saturation and large physiologic shunt.

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