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# Why Opioids and Sedatives May Prolong Life Rather Than Hasten Death After Ventilator Withdrawal in Critically Ill Patients

Jan Bakker, MD, PhD, Tim C. Jansen, MD, Alex Lima, MD, and Erwin J. O. Kompanje, MD, PhD

The process of death in patients in whom cardiorespiratory support is withdrawn is related to the occurrence of tissue hypoxia that results from an imbalance between the demand for oxygen and the delivery of oxygen to the organs. Limiting the demand for oxygen may thus delay the occurrence of tissue hypoxia. Because the demand for oxygen increases significantly

after ventilator withdrawal and because sedatives and opioids are known to decrease the demand for oxygen in patients with cardiorespiratory distress, these agents might thus actually prolong life rather than hasten death.

**Keywords:** palliative care; tissue hypoxia; opioids

The possible paradoxical effects of sedatives and opioids in dying patients still remain a matter of debate. Edwards<sup>1</sup> recently reported on the effects of these agents in dying patients: "Where they were expected to hasten death they seemed to prolong life." This discussion is important because the 2 effects can have serious consequences. A Dutch resident in anesthesiology was recently tried for murder after the administration of morphine and midazolam to a severely dyspneic patient.<sup>2</sup> After almost 2 years of trial, he was found innocent because the medical experts considered the dose of morphine and midazolam used was normal clinical practice in those circumstances. In addition, there is a good rationale why sedatives and analgesics at the end of life more likely prolong life than hasten death. To understand this, some basic pathophysiology applies.

## Coupling of Oxygen Delivery to Oxygen Demand

For vital organs to maintain adequate function, the oxygen received should meet its demand. Oxygen demand is related to the rate of metabolism in the organs and thus the amount of work performed. In normal circumstances, oxygen demand is equal to the amount of oxygen consumed. The transport of oxygen ( $DO_2$ ) to the organs is a function of the arterial oxygen saturation ( $SaO_2$ ), the arterial hemoglobin level (Hb), cardiac output (CO), and a constant ( $\kappa$ ), as shown in the formula:  $DO_2 = SaO_2 \times Hb \times CO \times \kappa$ .

When either arterial oxygen levels decrease (respiratory failure) or hemoglobin levels fall (hemorrhage), oxygen delivery to the organs can be maintained by an increase in cardiac output. Thus, the normal response to hypoxemia and bleeding is tachycardia in order to increase cardiac output. When cardiac output falls, we cannot compensate by increases in either arterial oxygen levels or hemoglobin levels. Only by extracting more oxygen from the blood can the organs meet their demand for oxygen.

When oxygen delivery decreases, oxygen demand is met (oxygen consumption remains stable) by an increase in the extraction of oxygen by the organs. In

From the Department of Intensive Care, Erasmus MC University Medical Center, Rotterdam, The Netherlands.

Address correspondence to: Jan. Bakker, MD, PhD, Erasmus MC University Medical Center, Room 625, PO Box 2040, 3000 CA Rotterdam, The Netherlands; e-mail: [jan.bakker@erasmusmc.nl](mailto:jan.bakker@erasmusmc.nl).

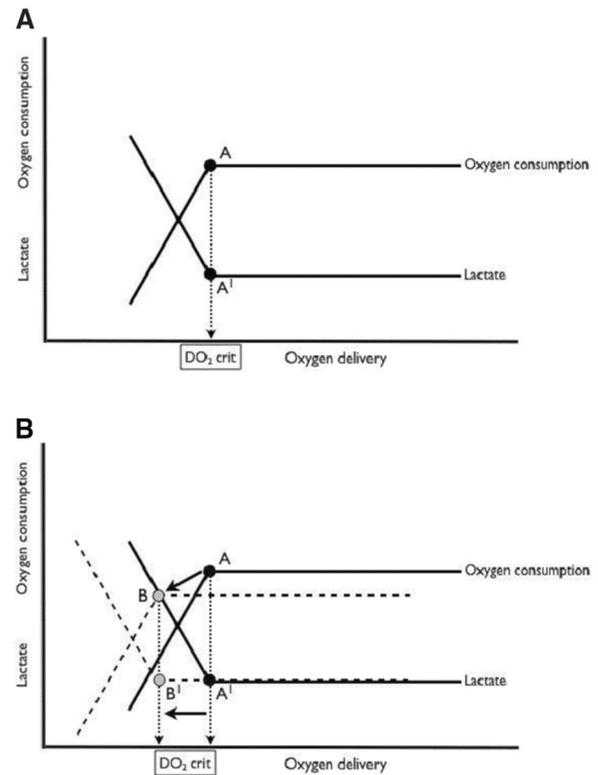
Figure 1A, the horizontal line in the relationship between oxygen delivery and oxygen consumption demonstrates this. When oxygen delivery decreases below a critical level ( $DO_2$  crit), oxygen consumption starts to fall and lactate levels start to increase, indicating the occurrence of anaerobic metabolism and tissue hypoxia. From both animal experiments and studies of dying humans, it is clear that severe decreases below the critical oxygen delivery level can only be tolerated for a limited time before anaerobic metabolism prevails, lactate levels start to rise, and the animal or patient dies.<sup>3,4</sup> When oxygen demand is decreased, the critical oxygen delivery level is decreased as well.<sup>5</sup> In Figure 1B, the interrupted line depicts this (decreased oxygen demand is illustrated by a lower oxygen consumption at base), and the critical oxygen delivery point is shifted to the left ( $A \rightarrow B$ ), so that lactate levels start to rise only at lower oxygen delivery levels ( $A^1 \rightarrow B^1$ ).

## The Process of Death

When a patient is disconnected from a mechanical ventilator, the duration of survival depends on several mechanisms. The dying process of the organs basically starts when the demand for oxygen is not met by an adequate delivery of oxygen. Because disconnection from the ventilator will have no influence on the hemoglobin level, it is mainly changes in arterial saturation or cardiac output, or both, that will result in changes in oxygen delivery to the organs and will thus affect the balance between oxygen demand and oxygen delivery. Two important possibilities then exist.

First, the patient is unable to breathe spontaneously. This is usually the case in patients with severe neurologic disease or when muscle relaxants have been administered to the patient. Severe hypoxemia (low arterial oxygen saturation) will rapidly develop in this situation. The cardiac output will first increase (tachycardia) so that the oxygen demand of the heart increases. Owing to the severe hypoxemia and the increased metabolic demand of the heart, cardiac arrest usually occurs rapidly, depending on the patient's premorbid cardiac condition.

Second, the patient is able to breathe spontaneously. In this case, the balance between oxygen demand and oxygen supply is crucial. In healthy volunteers, decreases in arterial oxygenation of up to 60% will not result in severe tissue hypoxia<sup>6</sup> owing to



**Figure 1.** (A). The relationship between the delivery of oxygen ( $DO_2$ ), lactate levels, and the consumption of oxygen. When oxygen delivery decreases to a critical level ( $DO_2$  crit), oxygen consumption falls and lactate levels start to rise. (B). When baseline oxygen consumption (oxygen demand) is decreased, the critical level of oxygen delivery is shifted left ( $A \rightarrow B$ ). The relationship of oxygen delivery, lactate levels, and oxygen consumption is not affected by the decrease in oxygen demand.

compensatory increases in cardiac output. In critically ill patients, disconnection from the ventilator during normal weaning procedures increases oxygen demand by as much as 25%.<sup>7</sup> The opposite effect, reducing oxygen demand by putting the patient on the ventilator, is probably an important mechanism in improving the survival in patients with cardiogenic shock.<sup>8</sup> Therefore, when increased work of breathing is necessary to maintain arterial oxygenation and when progressive hypoxemia increases the ventilatory drive, sedatives may reduce overall oxygen demand. Limited research in patients is available to support this. The administration of sedatives (midazolam and morphine) has been associated with decreases in oxygen demand and the attenuation of the cardiopulmonary response associated with increased work of breathing.<sup>9-11</sup> So when oxygen demand is

decreased, lower levels of oxygen delivery are tolerated before tissue hypoxia and vital organ dysfunction occurs (Figure 1B).

## Conclusion

In mechanically ventilated critically ill patients who are able to breathe spontaneously, a clear pathophysiologic rationale exists why opioids and sedatives may prolong life rather than hasten death after the ventilator is disconnected. These mechanisms also explain the improved survival when mechanical ventilation is applied in patients with acute cardiorespiratory failure.

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