# Permissive hypercapnia: From the ICU to the operating room

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Although the effect of permissive hypercapnia on hemodynamics and right ventricular function was previously reported in patients with acute respiratory distress syndrome, the effects of acute controlled hypercapnia on right ventricular function during one-lung ventilation have not yet been investigated systematically. Experimental evidence is conflicting concerning the pulmonary vasodilatory or vasoconstrictive effect of hypercapnic acidosis. The final effect of hypercapnic acidosis on physiological functions depends on the level of hypercapnia and the context of the individual (healthy vs. diseased).

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## Introduction

One-lung ventilation (OLV) in patients undergoing pulmonary resection is challenging and fraught of many complications. One of these complications is increased airway pressure of the dependent lung with potential risk for barotrauma [1].

During OLV, tidal volume (Vt) is frequently maintained at the same level as during two-lung ventilation without positive end-expiratory pressure (PEEP), targeting normalization of $CO_2$ [2,3]. This maintenance corresponds to high-volume ventilation with potentially deleterious effects, even for a period of less than 90 min [4,5]. Normalizing $CO_2$ at the expense of inducing undue lung stretch may not be appropriate.

In mechanically ventilated ICU patients, reduced Vt with an associated increased $CO_2$ (permissive hypercapnia) has become an accepted practice [6,7]. Recently, Michelet *et al*. [8] demonstrated that the protective ventilatory strategy based on the reduction of Vt is beneficial during OLV.

The increased hypoxic pulmonary vasoconstriction (HPV) during hypercapnic acidosis (HCA) is beneficial to lung gas exchange by improving ventilation–perfusion matching and preserving the capillary barrier function. These effects seem to be linked to the NO-mediated pathways [9].

Although the effect of permissive hypercapnia on hemodynamics and right ventricular (RV) function was previously reported in patients with acute respiratory distress syndrome (ARDS) [10], the effects of acute controlled hypercapnia on RV function during OLV have not yet been investigated systematically.

Potentially harmful consequences of permissive hypercapnia include pulmonary vasoconstriction and pulmonary hypertension, proarrhythmic effects of increased discharge of the sympathetic nervous system, and cerebral vasodilation yielding increased intracranial pressure. However, experimental data have suggested that permissive hypercapnia is not only safe, but also potentially beneficial. Nonetheless, permissive hypercapnia should probably be used with caution in patients with heart disease and is relatively contraindicated in those with elevated intracranial pressure [11].

HCA has a myriad of effects on many physiological processes. The recognition of these effects is important as it will affect the decision whether or not to allow the development of HCA in a specific patient. As outlined below, the final effect of HCA on physiological functions depends on the level of hypercapnia, the context of the individual (healthy vs. diseased), and many other factors [12].

## Hypercapnic acidosis and oxygenation

The beneficial effects of HCA in increasing arterial and tissue oxygenation is evident from multiple in-vivo studies [13,14] and have been demonstrated in healthy humans as well [15]. HCA can improve tissue oxygenation by several mechanisms. First, a rightward shift of the oxyhemoglobin dissociation curve during acute respiratory acidosis decreases the affinity of hemoglobin for oxygen and facilitates oxygen release to the tissues (the Bohr effect) [16]. Second, HCA causes vasodilatation in microvessels, promoting oxygen delivery and tissue perfusion. However, high concentrations of $PaCO_2$ (>100 mmHg) will surpass the beneficial vasodilatory effects of HCA and result

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in vasoconstriction [17]. Third, HCA improves ventilation–perfusion (V/Q) matching by potentiating HPV [18,14]. However, HPV could be partly blunted by inhalational anesthetics, but there is no clear evidence to support that inhalational agents could attenuate or abolish the effect of HCA on HPV. Fourth, as cardiac output is one of the major determinants of peripheral oxygen delivery, one can expect that a $CO_2$-mediated increase in cardiac output augments peripheral oxygen delivery. However, an increase in cardiac output results in an increase in mixed venous oxygen tension, which may lead to an increase in pulmonary shunting due to attenuation of HPV [19,20].

#### Hypercapnic acidosis and pulmonary compliance

It has been demonstrated in experimental studies that pulmonary compliance is improved by HCA. This may be explained by the pH-mediated effect of HCA in improving surfactant secretion and its surface tension-lowering properties [21,22].

#### Hypercapnic acidosis and pulmonary vascular tone

Increases in pulmonary vascular tone may have particularly unfavorable consequences in patients with pulmonary hypertension. Experimental evidence is conflicting concerning the pulmonary vasodilatory or vasoconstrictive effect of HCA [23–25]. These apparent opposing effects may be attributable to the presence or absence of pH buffer resulting in pulmonary vasodilatation or vasoconstriction, respectively [24–26].

However, clinical studies demonstrate that HCA causes an increase in mean pulmonary arterial pressure in ARDS [27,28]. Recently, Mekontso *et al.* [10] showed a lower RV stroke index in patients with severe ARDS who were ventilated with higher PEEP (10–11 mmHg) at a constant plateau pressure that subsequently led to HCA (pH 7.17–7.20, $PaCO_2$ 70–75 mmHg). An increase in pulmonary vascular resistance was postulated, but no objective measurements were performed. Multivariate analysis demonstrated that pH, *per se*, and not $CO_2$ or PEEP, was responsible for the impaired RV function [10]. Therefore, caution is warranted with the use of 'permissive' or 'therapeutic' HCA in patients with pulmonary hypertension and depressed RV function.

## Hypercapnic acidosis and cardiovascular system

#### Effects on cardiac output

HCA has a direct suppressive effect on cardiac contractility, but it can lead to a net increase in cardiac output by several mechanisms, as has been demonstrated in both animal and human studies [15,17,18,28–30]. First, sympathetically mediated release of catecholamines due to neuroadrenal stimulation results in an increase in end-systolic volume and venous return [31,30]. In addition to an increase in heart rate, HCA induces ATP-sensitive $K^+$ channel-mediated vasodilation, as has been demonstrated for the brain vasculature and coronary vessels [32,33], which could decrease left ventricular afterload. An increase in 10–12 mmHg in $PaCO_2$ increases the cardiac index by 14% in the critically ill and healthy mechanically ventilated patients [15,28]. In the clinical setting, however, care should be taken with patients exhibiting depressed myocardial function.

#### Effects on the myocardium

Acidosis has protective effects against myocardial ischemia–reperfusion injury [34,35]. Hydrogen ions inhibit $Ca^{2+}$ influx into the myocardial fiber, which decreases myocardial contractility and oxygen demand, leading to less tissue injury during myocardial ischemia [35,36]. Furthermore, hypercapnia causes coronary vasodilatation, which may be of further benefit during the period of reperfusion [37]. These protective effects of hypercapnia can be of pivotal importance in the treatment of patients undergoing coronary artery bypass grafting with extracorporeal circulation and subsequently experiencing myocardial suppression.

Perhaps, the most comprehensive study on the effects of hypercapnia on pulmonary circulation and the heart was conducted by Kiely *et al.* [38] in healthy young volunteers, using a Doppler ultrasound control method. The volunteers were tested before and after inhaling a $CO_2$-rich mixture with the aim of achieving hypercapnia of 55–60 mmHg with the measurement of numerous useful parameters to assess the response of pulmonary circulation, peripheral circulation, and the heart. In the systemic circulation, an increase in CO, SV, HR, SBP, DBP, and MAP has been observed with a slight and insignificant reduction in SVR. Changes of this kind were already observed 50 years ago by Price [39] and 35 years ago by Cullen and Enger [40]. However, whereas previous experiments on isolated hearts demonstrated a depressant effect for hypercapnia [41], in this study no such effect was found. In fact, increased aortic flow and peak flow did not change with hypercapnia, meaning that this neither reduced nor increased myocardial contractility.

The direct effect of HCA on the heart and vascular smooth muscle is to reduce contractility. However, these direct effects are opposed by a neurohumeral effect, thus resulting in an increase in sympathomimetic output. This leads to an increase in HR, systemic vasodilatation, and decrease in left ventricular afterload, which results in an increase in CO [40].

Hypercapnia targeting $CO_2$ 50–70 mmHg was associated with increased cardiac output, central venous $O_2$, and arterial $O_2$ tension in patients undergoing video-assisted thoracoscopic patent ductus arteriosus closure using OLV without any deleterious cardiopulmonary effects [42].

## Conclusion

Permissive hypercapnia should be a routine component of OLV management. With a reasonable cardiovascular reserve, and in particular RV function, $PaCO_2$ levels up to 60–70 mmHg are likely to be well tolerated in the short-term and are clearly beneficial in terms of lung injury avoidance and attenuation. However, more research is needed to investigate the effect of hypercapnia on the right ventricle. The final effect of HCA on physiological functions depends on the level of hypercapnia and the context of the individual.

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### Conflicts of interest

There are no conflicts of interest.

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