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Metabolism and physiological effects of carbon dioxide. Implications in anaesthetic management

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Abstract

Background: Carbon dioxide is a normal by-product of aerobic metabolism that maintains the equilibrium of respiratory act, being eliminated from the lungs. Despite of an increasing number of researches concerning carbon dioxide metabolism and its effects on human homeostasis, there are still discussions about carbon dioxide metabolism, physiology and its implication in anaesthetic management, ICU, critically ill patient. The use of mild to moderate hypercapnia during general anaesthesia and in mechanically ventilated patients is growing, based on scientific researches of last years.

Material and methods: There has been scientifically evaluated data from PubMed, 2002-2017. Key words used in search are: "carbon dioxide", "ventilation", "metabolism", "gas change". There were selected articles, taking in consideration their title, and chosen abstracts. The article contains a qualitative analysis and synthesis of the recommendation, concerning anaesthetic management and metabolism of carbon dioxide.

Conclusions: Carbon dioxide metabolism and its anaesthetic management, represents a challenge that will be actual for many years in future. The amount of controversial studies about effects of carbon dioxide on patients under general anaesthesia or mechanical ventilation, determined us to perform a review of literature, and evaluate it.

There are known facts about carbon dioxide metabolism, such as normal values, how it is produced in human body, how it is evacuated, effects on cardiovascular, nervous systems, and still there are many controversial studies on that topic, that determine to study it more and find new research results.

Key words: carbon dioxide, ventilation, metabolism, gas change.

Introduction

Arterial carbon dioxide tension represents the balance between the production and elimination of carbon dioxide, and in healthy persons, it is maintained within narrow physiologic limits. EtCO_2 represents the partial pressure or maximal concentration of carbon dioxide (CO_2) at the end of an exhaled breath, which is expressed as a percentage of CO_2 or mmHg [3-6]. The normocapnic values are 5% to 6% CO_2 , which is equivalent to 35-45 mmHg. CO_2 reflects cardiac output (CO) and pulmonary blood flow as the gas is transported by the venous system to the right side of the heart and then pumped to the lungs by the right ventricles [3,4]. When CO_2 diffuses out of the lungs into the exhaled air, a capnometer measures the partial pressure or maximal concentration of CO_2 at the end of exhalation.

Carbon dioxide being a by-product of aerobic metabolism, has a significant role in ventilation process of lungs. For many years CO_2 was considered a harmful metabolite that was no need to be maintained in human organism, so hypocapnia was maintained during general anaesthesia. It was considered that hypocapnia with induced vasoconstriction provided during general anaesthesia, from economical reasons was beneficial. Only during past ten years, it was determined that mild to middle hypercapnia induced to patients that suffer of acute respiratory distress syndrome (ARDS), resulted in significant improvement of their medical condition. After a few studies concerning effects of hypercapnia, the interest to this topic started to grow. Nowadays, there is increasing amount of studies about effects of mild to middle hypercapnia for the Intensive Care Unit (ICU) patients or effects of hypercapnia during general anaesthesia.

Material and methods

The article contains a scientific review of carbon dioxide metabolism from PubMed that was published in 2002-2017. There were selected prospective studies, guidelines, textbooks of respiratory physiology, and anaesthetic management. Key words used in search are: carbon dioxide, ventilation, metabolism, gas change. The article contains a qualitative analysis and synthesis of the recommendations, concerning anaesthetic management and metabolism of carbon dioxide. There were selected articles, taking in consideration their title, and chosen abstracts. In the process of searching by title using the key word, there have been found 3200 results. After selecting period of years 2002-2017, 737 results appeared.

Results

Carbon dioxide (CO_2) is a normal by-product of aerobic metabolism in human body (fig. 1). Increased CO_2 in the body results in important physiological responses throughout the body. CO_2 is a potent stimulus of pulmonary minute ventilation and it acts by stimulating chemoreceptors in the carotid bodies and respiratory control centres in the brain and brainstem, that change in ventilation in response to CO_2 production that keeps alveolar pressure of CO_2 (PCO_2) in dynamic equilibrium with metabolically produced CO_2 [2,3]. Carbon dioxide is also a potent stimulus of cerebral vasodilation and blood flow.

Hypercarbia can result from hypoventilation: low breathing rate allows build-up of CO_2 (e.g., deliberate "skip-breathing" by SCUBA divers), malfunctioning respirator can lead to increased rebreathing of CO_2 , increase in the dead space of breathing apparatus or increased alveolar dead space (e.g.,

pulmonary embolism), increased breathing resistance of respiratory protective device (RPD) leading to a reduction in breathing frequency.

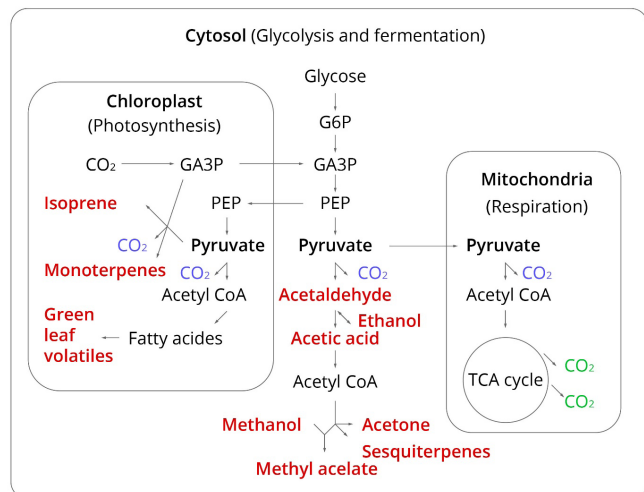


Fig. 1. Aerobic metabolism in human body, according to slideshare.com.

In addition, a high CO₂ in human body can induce visual disturbances, headache, and reduction in reasoning ability, a sense of “air hunger” or dyspnoea.

Elevated level of CO₂ in human blood can act as an anaesthetic and can cause unconsciousness inducing inert gas narcosis similar to nitrous oxide. CO₂ can alter the intracellular pH thus having effects on metabolism (also probable mechanism for inert gas narcotic effect) [8, 9, 10]. In its simplest form, the partial pressure of arterial carbon dioxide (PaCO₂) reflects the balance between the production and elimination of carbon dioxide (CO₂), as described by the following formula:

$$\text{PaCO}_2 \text{ is proportional to } \frac{\text{CO}_2 \text{ production}}{\text{CO}_2 \text{ elimination}} + \text{inspired CO}_2.$$

End tidal CO₂ (EtCO₂) represents the partial pressure or maximal concentration of CO₂ at the end of exhalation. CO₂ reflects cellular metabolism. There are four main stages of normal physiology of CO₂: production, transport, buffering and elimination.

Production: CO₂ is a metabolic by-product of aerobic cell metabolism. As the intracellular CO₂ increases, CO₂ diffuses out into the tissue capillaries and is carried by the venous circulation to the lungs, where it diffuses from pulmonary capillaries into the alveoli. The partial pressure of CO₂ of venous blood entering pulmonary capillaries is normally 45 mmHg; the partial alveolar pressure of CO₂ (PACO₂) is normally 40 mmHg [6]. The pressure difference of 5 mmHg will cause all the required CO₂ to diffuse out of pulmonary capillaries into the alveoli.

Transport: The second stage is CO₂ transport, which is a way of maintaining the CO₂ tension of arterial blood at approximately 35-45 mmHg despite high CO₂ production.

Buffering: The third stage is where the buffer action of

haemoglobin and pulmonary blood flow maintain the normal level of CO₂ tension by eliminating the excess CO₂. CO₂ can either be carried, dissolved or combined with water (H₂O) to form carbonic acid (H₂CO₃), which can dissociate to hydrogen ions (H⁺) and bicarbonate ions (HCO₃⁻): (CO₂ + H₂O <=> H₂CO₃ <=> H⁺ + HCO₃⁻). The hydrogen ions are buffered by haemoglobin, and the bicarbonate ions are transported into the blood. This mechanism accounts for 90% of CO₂ transport.

Elimination: The fourth stage involves CO₂ elimination by alveolar ventilation under the control of the respiratory center. This process allows the diffusion of CO₂ from blood to the alveoli where the partial alveolar pressure of CO₂ is lower than the tissue pressure [10, 11].

During normal circulatory condition with equal ventilation/perfusion ratio (V/Q) relationship, PaCO₂ is closely comparable to PaCO₂ and EtCO₂; therefore, PaCO₂ is equivalent to EtCO₂. The difference between PaCO₂ and EtCO₂ is known as the CO₂ gradient [13-15]. The normal EtCO₂ is about 38 mmHg at 760 mmHg of atmosphere with less than 6 mmHg gradients between PaCO₂ and EtCO₂.

The principle determinants of EtCO₂ are: alveolar ventilation, pulmonary perfusion (cardiac output) and CO₂ production.

During acutely low cardiac output state as in cardiac arrest, decreased pulmonary blood flow becomes the primary determinant resulting in abrupt decrease of EtCO₂ [16, 18]. Changes in alveolar ventilation can also influence EtCO₂ as PACO₂ closely approximates PaCO₂ and EtCO₂. If ventilation and chest compressions are constant with the assumption that CO₂ production is uniform, then the change in EtCO₂ reflects the changes in systemic and pulmonary blood flow. Ultimately, EtCO₂ could be used as a quantitative index of evaluating adequacy of ventilation and pulmonary blood flow during CPR.

Monitoring the carbon dioxide metabolism during general anaesthesia represents a key-factor in managing an adequate anaesthesia. A lower level of EtCO₂ than 35 mmHg is being considered hypocapnia [17,18,19]. A level of EtCO₂ 35-45 mmHg is determined as normocapnia, and levels more than 45 mmHg, are considered hypercapnia.

Hypocapnia has been considered during general anaesthesia for the purposes of suppressing respiratory effort and reducing anaesthetic requirements. Hypocapnia and associated alkalosis, however, have physiological effects that may be detrimental. Such effects include decreased cerebral blood flow and cognitive function, increased airway resistance and pulmonary cellular dysfunction, vasoconstriction and increased myocardial oxygen demand, hypercoagulability, and dysrhythmias. In contrast, hypercapnia may have beneficial effects including increased cardiac index, oxygen delivery and tissue (e.g. surgical site) oxygen tension, and attenuation of lung injury. As these effects may influence postoperative complications, postoperative recovery, or both, there could be a relationship between intraoperative end-tidal carbon dioxide (EtCO₂)

and clinical outcomes [19]. Moderate to severe hypocapnia (partial pressure of arterial carbon dioxide, 20 to 25 mm Hg) was, an adjunct to general anaesthesia.

Its proposed advantages include the minimization of spontaneous respiratory effort and a reduced requirement for sedative, analgesic, and muscle-relaxant medications.

The latter advantage may explain the widespread use of intraoperative hyperventilation in the 1960s as a means of reducing the use of anaesthetic medications and thus avoiding fetal depression immediately after caesarean section. The use of hypocapnia during general anaesthesia remained common for at least the next two decades.

Hyperventilation and hypocapnia decrease cardiac output, which in turn decreases blood flow and oxygen tension in brain and splanchnic organs. Hypocapnia also shifts the oxyhaemoglobin curve leftward and restricts oxygen unloading at the tissue level [19].

Hypercapnia, in contrast, increases cardiac output and decreases systemic vascular resistance and oxygen extraction; it thus increases oxygen availability to tissue. Hypercapnia also causes a complex interaction between altered cardiac output, hypoxic pulmonary vasoconstriction, and intrapulmonary shunt with the result being a net increase in PaO_2 at a given inspired oxygen concentration. Consistent with these observations, we recently demonstrated that short periods of hypercapnia improve tissue oxygenation in anaesthetised volunteers.

Ventilation is the movement of gases between the atmosphere and the alveoli. This must be distinguished from oxygenation. While ventilation might be normal, oxygenation can be inadequate if either the gas inhaled is lacking in oxygen or perfusion to the pulmonary alveoli is compromised. Ventilation consists of two phases: inspiration and expiration. Inspiration delivers oxygen to the alveoli and expiration delivers carbon dioxide, the by-product of cell metabolism, to the environment [20]. Although ventilation can be initiated voluntarily, it is largely under the control of the respiratory centres of the medulla where chemoreceptors respond to elevations in hydrogen ion concentration (pH) in the following manner: Carbon dioxide (CO_2) diffuses from the blood to the cerebrospinal fluid in the brain and combines with water to form carbonic acid. The acid dissociates into bicarbonate and hydrogen ions ($\text{CO}_2 + \text{H}_2\text{O}$

$\text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$). Although the chemoreceptors actually respond to hydrogen ions, the mechanism is referred to as *hypercapnic drive* because it is activated as serum carbon dioxide tensions elevate. The respiratory centre can also be stimulated by neural impulses generated in the peripheral chemoreceptors of the aortic and carotid bodies. These receptors respond primarily to a decline in PaO_2 , and they are referred to as *hypoxemic drive*. Normally this mechanism assumes a secondary role to central hypercapnic drive, but assumes greater significance when central receptors become tolerant to elevated CO_2 levels that occur with disorders such as chronic obstructive lung disease [20].

Like oxygen, the smallest portion of carbon dioxide

in blood is in the free state. Most is transported as bicarbonate ion (70%), and 23% is bound to haemoglobin as carbaminohemoglobin. Only 7% of total carbon dioxide is dissolved in blood and produces a gas tension, designated PaCO_2 . Normal PaCO_2 is approximately 40 mm Hg, and it can be measured in arterial blood gas studies along with PaO_2 , as described above.

While PaO_2 is used to assess oxygenation, PaCO_2 is the true measure of ventilation. As stated above, ventilation may be normal but the patient can be hypoxemic if the gas inhaled is deficient in oxygen or pulmonary perfusion is compromised. Conversely, a patient who is hypoventilating may be well oxygenated if he or she is breathing a gas mixture enriched with oxygen. However, PaCO_2 will invariably elevate if ventilation is inadequate because carbon dioxide is not being eliminated. To summarize, a low PaO_2 indicates poor oxygenation (hypoxemia) while an elevated PaCO_2 (hypercarbia) indicates hypoventilation [21].

Capnometry is the measurement of carbon dioxide concentration during the respiratory cycle. It uses infrared technology to analyse carbon dioxide in exhaled gas. There are multiple options to facilitate sampling of carbon dioxide. The most accurate readings are those obtained by sampling gases in the endotracheal tube of an intubated patient. However, during moderate and deep sedation the patient is not intubated, so other devices have been developed for gas sampling. Special nasal cannulas, designed to provide supplemental oxygen during sedation, also have a sampling line included. Cannulas without this feature can be modified by placing an intravenous catheter through one of the nasal prongs and attaching the monitor sampling line to the catheter hub [22].

Capnography is the proper term for those monitors that display a continuous waveform reflecting inspiration and expiration. While capnometers and capnographs both display numeric values for EtCO_2 and respiratory rate, capnography is preferred because visualization of the waveform allows continuous assessment of the depth and frequency of each ventilatory cycle. Respiratory depression produces a reduction in number of waveforms while obstructions alter the shape and height of each waveform [20, 21].

Discussion

Intraoperative hyperventilation to induce hypocapnia has historically been common practice and has physiological effects that may be detrimental. In contrast, hypercapnia has effects that may be beneficial. As these effects may influence postoperative recovery, was investigated the association between variations in intraoperative carbon dioxide and length of hospital stay in patients who had elective colon resections and hysterectomies. There was a significant association between higher intraoperative EtCO_2 and shorter LOS after colon resection and open hysterectomy [22]. Also hypercapnia, increases cardiac output and decreases systemic vascular resistance and oxygen extraction; it thus increases oxygen availability to tissue. Hypercapnia also

causes a complex interaction between altered cardiac output, hypoxic pulmonary vasoconstriction, and intrapulmonary shunt with the result being a net increase in PaO₂ at a given inspired oxygen concentration. Consistent with these observations, recently demonstrated that short periods of hypercapnia improve tissue oxygenation in anaesthetised volunteers [3].

Hypercapnic acidosis, common in mechanically ventilated patients, has been reported to exert both beneficial and harmful effects in models of lung injury. Study on effects of hypercapnic acidosis on mitogen-activated protein kinase (MAPK) activation, determined that p44/42 MAPK activation in a murine model of ventilator-induced lung injury (VILI) correlated with injury and was reduced in hypercapnia models [23].

Continuing studies on effects of carbon dioxide, in anesthetic management of patients, may improve the quality of perioperative management. The outcomes could open new strategies for anaesthetic management and critically ill patients with pulmonary disease, considering mechanical ventilation.

Conclusions

Metabolism of carbon dioxide is a part of respiratory physiological act. There are known facts about carbon dioxide metabolism, such as normal values, how it is produced in human body, how it is evacuated, effects on cardio-vascular and nervous systems, and still there are many controversial studies, that determine to study more and find new research results.

Whereas oxygen is necessary for life and vital for aerobic metabolism, and carbon dioxide is a normal product of aerobic metabolism and is an important regulator of physiological function.

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