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EDITORIAL

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End-tidal CO_2: physiology in pursuit of clinical applications

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Carbon dioxide (CO_2) is produced by aerobic metabolism. Fever, sepsis, physical activity including shivering, hyperthyroidism, trauma, burns, and high carbohydrate intake increase its production. Sedation and paralysis, hypothermia, and hypothyroidism decrease CO_2 production. Carbon dioxide is transported from cells to the lungs predominantly as bicarbonate with 5–10% transported dissolved in plasma and another 5–10% transported as carbamino compounds. Carbon dioxide's elimination by the lungs constitutes ventilation. Exhaled CO_2 monitoring has evolved in two directions, monitoring of intubation and ventilation, and as an indirect indicator of cardiac output.

Exhaled CO_2 monitoring has been used clinically for more then a decade to monitor the success or failure of intubation, and as a safety feature for patients undergoing mechanical ventilation. The simplest way to determine the presence or absence of CO_2 involves colorimetric changes of pH sensitive paper indicating the presence of CO_2; the Nellcor-Puritan-Bennett EasyCap uses this principle to demonstrate successful intubation of the larynx. Most monitoring devices incorporate the transmission of infrared light to measure the concentration of CO_2 present in exhaled gas. This data can be presented digitally or graphically (capnometry and capnography, respectively) providing more information, which can be used for monitoring purposes.

In hemodynamically stable conditions, end-tidal CO_2 ($ETCO_2$) reflects the amount of CO_2 delivered to the lungs. $ETCO_2$ measurement directly correlates with arterial CO_2 concentration with the normal arterial–$ETCO_2$ difference ranging from 4–6 mmHg [1]. Similar to arterial CO_2, $ETCO_2$ reflects minute ventilation. Rising levels of CO_2 may indicate: decreased ventilation from ventilator malfunction, neuromuscular disease, etc.; increased CO_2 production from fever, shivering, malignant hyperthermia, and sepsis; and decreased effective alveolar ventilation from bronchospasm. Falling levels of $ETCO_2$ can indicate an endotracheal tube cuff-leak, hypothermia, or hyperventilation. Complete absence of CO_2 may indicate a ventilator disconnection, complete endotracheal tube obstruction, or an esophageal intubation. Unfortunately, the correlation between $ETCO_2$ and $PaCO_2$ is not perfect. The difference between the two measurements may increase or decrease in an unpredictable fashion, occasionally even tracking in opposite directions [2, 3, 4]. Despite these limitations, $ETCO_2$ monitoring may still be useful following trends in stable patients, perhaps limiting the amount of blood gases needed [5].

In this issue of *Intensive Care Medicine*, Dubin et al. [6] elegantly demonstrate the relationship of $ETCO_2$ measured with a capnograph ($PETCO_{2)}$ to cardiac output (CO) determined using pulmonary artery electromagnetic flow probes in a canine hemorrhagic shock model. After baseline measurements, a cycle of removing 6 ml/kg of blood followed by 10 min for equilibration of blood pressure continued until a circulatory crisis of rapidly falling blood pressure occurred. The absolute amount of blood or percentage of total blood required to precipitate this crisis is not defined. Similarly, the definition of "circulatory crisis" is not defined. Despite these shortcomings, there is sufficient information to be comfortable with the model and the results obtained. $ETCO_2$ clearly correlated with cardiac output with the greatest decrease in $ETCO_2$ in the lowest flow states.

This work further substantiates a considerable amount of animal and human data, demonstrating the relationship between low-output states and the arterio-venous CO_2 gradient.

Adrogue et al. [7] demonstrated an excellent correlation of $ETCO_2$ and cardiac output in dogs subjected to low-flow states induced by pharmacologic vasodilatation, hemorrhage, increased intrathoracic pressure using PEEP, and cardiac arrest from ventricular fibrillation or pericardial tamponade. They too found that the arterial–$ETCO_2$ gradient increased as cardiac output declined; the greatest differences were noted when the cardiac output was severely compromised. Idris et al. [8] using a ventricular-assist device to control cardiac output noted the same correlation in very low cardiac output states. Adrogue [9], Falk [10], and Chopin [11] demonstrated this relationship in humans suffering from congestive heart failure, sepsis, cardiac arrest, and pulmonary embolism. Unfortunately, compensatory mechanisms preserve relatively normal $ETCO_2$ values until moderate to severe falls in cardiac output and hemodynamic instability are seen, rendering $ETCO_2$ monitoring relatively insensitive to these conditions. Conversely, an increased arterial-$ETCO_2$ gradient is very sensitive but not specific for pulmonary embolism [11].

During a cardiac arrest, $ETCO_2$ falls to very low levels reflecting the very low cardiac output achieved with CPR. Paradoxically, due to poor clearance of respiratory acids and buffering with bicarbonate, the tissue and venous levels of CO_2 may increase to several hundred mmHg [12, 13, 14]. The $ETCO_2$ achieved during ACLS has been shown to reliably predict outcome from cardiac arrest. Higher levels reflect better cardiac output and a greater likelihood of successful resuscitation [15, 16]. Unfortunately, this is not accurate enough to predict survival with confidence. Rather than use a high $ETCO_2$ to predict survival, we studied the utility of a low $ETCO_2$ to predict mortality. In cardiac arrest due to pulseless electrical activity, we showed [17] that if the $ETCO_2$ was < 10 mmHg after 20 min of ACLS, there were no survivors. If these findings are confirmed, prolonged failure to achieve an adequate cardiac output as reflected in the $ETCO_2$ may allow discontinuation of ineffective CPR.

Thus, under what circumstances is $ETCO_2$ monitoring likely to be useful? Abrupt changes of $ETCO_2$ may provide an alert to an adverse event having taken place. However, there are so many redundant monitoring systems in most intensive care units that changes in $ETCO_2$ may only marginally increase our ability to detect these events. Therefore, I believe that $ETCO_2$ monitoring will not find a major role for the diagnosis or monitoring of these conditions though the astute clinician will certainly not ignore this useful information.

However, there is no question that detection of $ETCO_2$ in exhaled gas has substantially improved our ability to detect the correct or incorrect placement of endotracheal tubes. Though not perfect, the continued detection of CO_2 after a patient has been intubated is the single best confirmatory test of tube placement. Absence of CO_2 in exhaled breath mandates confirmation of endotracheal tube placement and a thorough evaluation of the patients' condition.

Finally, a substantial body of literature exists to support the measurement of $ETCO_2$ to help guide resuscitative efforts during CPR. If $ETCO_2$ monitoring becomes incorporated into ACLS algorithms to help determine when to stop (or continue) resuscitative efforts, $ETCO_2$ may have found a second niche where it provides unique, invaluable information. For all other purposes, $ETCO_2$ monitoring provides useful, additional information but is not sufficient as an independent monitoring system/diagnostic device to change our current practice.

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