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Review

Capnography during cardiac arrest

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ABSTRACT

Successful resuscitation from cardiac arrest depends on provision of adequate blood flow to vital organs generated by cardiopulmonary resuscitation (CPR). Measurement of end-tidal expiratory pressure of carbon dioxide (ETCO2) using capnography provides a noninvasive estimate of cardiac output and organ perfusion during cardiac arrest and can therefore be used to monitor the quality of CPR and predict return of spontaneous circulation (ROSC). In clinical observational studies, mean ETCO2 levels in patients with ROSC are higher than those in patients with no ROSC. In prolonged out of hospital cardiac arrest, ETCO2 levels < 10 mmHg are consistently associated with a poor outcome, while levels above this threshold have been suggested as a criterion for considering patients for rescue extracorporeal resuscitation. An abrupt rise of ETCO2 during CPR suggests that ROSC has occurred. Finally, detection of CO2 in exhaled air following intubation is the most specific criterion for confirming endotracheal tube placement during CPR. The aetiology of cardiac arrest, variations in ventilation patterns during CPR, and the effects of drugs such as adrenaline or sodium bicarbonate administered as a bolus may significantly affect ETCO2 levels and its clinical significance. While identifying ETCO2 as a useful monitoring tool during resuscitation, current guidelines for advanced life support recommend against using ETCO2 values in isolation for decision making in cardiac arrest management.

Introduction

End-tidal carbon dioxide (ETCO2) is the partial pressure of carbon dioxide (PCO2) in the exhaled air measured at the end of expiration. CO2 is produced in perfused tissues by aerobic metabolism, it diffuses from the cells into the blood and is transported by the venous return to the lungs, where it is removed by ventilation. The major determinants of ETCO2 therefore include CO2 production, cardiac output (CO), lung perfusion and alveolar ventilation [1].

Capnography represents a continuous, non-invasive measurement of PCO2 in the exhaled air during the breathing cycle. The correspondent waveform is called a capnogram (Fig. 1).

In the typical capnogram ETCO2 is the value recorded at the end of the plateau phase and it is the one which better reflects the alveolar PCO2. Normally, ETCO2 is around 5 mmHg lower than PCO2 in the arterial blood (PaCO2). This gradient increases when there is a ventilation/perfusion mismatch in the lung that may occur because of pulmonary embolism or lung hypoperfusion during cardiac arrest [2].

ETCO2 for monitoring the effectiveness of cardiopulmonary resuscitation

In patients with cardiac arrest, cardiopulmonary resuscitation (CPR) temporarily restores CO. Both experimental [3,4] and clinical [5] studies have shown that survival from cardiac arrest depends on provision of adequate perfusion to vital organs. However, direct measurement of organ blood flow during CPR is not clinically feasible. ETCO2 represents a non-invasive measurement of the effectiveness of CPR in terms of blood flow that is generated and the potential of successful resuscitation.

In an experimental porcine model of cardiac arrest, Gudipati et al. [6] showed that ETCO2 changes paralleled those of cardiac index (CI) during cardiac arrest and subsequent CPR (Fig. 2). When ventricular fibrillation was induced, ETCO2 dropped to zero along with CI. During CPR, ETCO2 was about 25% of pre-arrest values, as was CI generated by CPR. After successful defibrillation and return of spontaneous circulation (ROSC), ETCO2 increased rapidly, exceeding its pre-arrest values. This ETCO2 “overshoot” did not correspond to a proportional increase of CI, and it could be interpreted as a CO2 washout from tissues that had been poorly perfused during cardiac arrest.

Experimental studies demonstrated that during CPR ETCO2...

Another important quality target of CPR is avoiding hyperventilation. Another caveat for ETCO₂ as a detector of correct intubation is that it does not discriminate between tracheal and bronchial placement of the tube. For these reasons, clinical assessment with bilateral chest auscultation is essential. The 2015 ERC ALS guidelines [13] recommend using waveform capnography in addition to clinical assessment to confirm and continuously monitor endotracheal tube placement.

ETCO₂ to detect ROSC

ROSC is associated with a significant increase of ETCO₂ (Fig. 2), which raises up to a level three times above the values during CPR and then slowly declines to a stable value in all patients that maintain ROSC [24]. ETCO₂ monitoring can therefore help detect ROSC during resuscitation to avoid continuing unnecessary chest compression. On the other side, however, inappropriate interruptions of CPR should also be avoided, since they are detrimental to defibrillation success and survival [19,25,26]. Therefore, when detecting occurrence of ROSC, a high level of specificity (i.e., low rates of false positive results) are required.
In a retrospective case control study conducted on 108 OHCAs, Pokorna et al. [28] showed that a sudden increase of ETCO2 value of > 10 mmHg had 80% sensitivity but only 40% specificity in indicating that ROSC had occurred. In a subsequent prospective, cross-sectional study in 178 non-traumatic OHCAs, Lui et al. [29] showed that an ETCO2 rise ≥ 10 mmHg during CPR had 33% [95%CI 22–47%] sensitivity and 97% [95%CI 91–99%] specificity to detect ROSC. However, the median delay time between that 10-mmHg ETCO2 increase and the subsequent ROSC, however, was 12 min, much longer than the 2 min interval between two subsequent pulse checks as per the ALS algorithm.

The ERC ALS 2015 guidelines [3] indicate that ETCO2 can be a marker of ROSC during CPR and suggest checking electrocardiogram for presence of an organized rhythm when a rise in ETCO2 occurs. However, no specific ETCO2 threshold for interrupting CPR could be recommended.

ETCO2 to predict survival from cardiac arrest

Since ETCO2 is expected to reflect organ perfusion during CPR, it may not only represent a target of resuscitation, but also a predictor indicating when prolonged CPR is futile. In 1997, Levine et al. [30] investigated on the association between ETCO2 measured after 20 min of ALS and survival to hospital admission in 150 adults with OHCA from primary cardiac cause associated to pulseless electrical activity (PEA). Results showed that no patient with ETCO2 ≤ 10 mmHg after 20 min of ALS survived to hospital admission, while all patients with ETCO2 > 10 mmHg survived, which translated in 100% sensitivity and specificity for prediction of pre-hospital ROSC. These results were confirmed in a larger subsequent study from Kolar et al. [31] on 737 OHCAs from all rhythms using a ≥ 14.3 mmHg threshold at 20 min. The study also measured ETCO2 at 0, 10, and 15 min and showed that no patient with < 10 mmHg ETCO2 survived at any time.

ETCO2 has also been investigated as a predictor of ROSC at earlier stages of resuscitation, when it could be even more clinically useful. However, evidence shows that in this case its accuracy is generally lower. In the study from Levine et al. [30] mentioned above, initial ETCO2 values did not differ between survivors and non-survivors (12.3 ± 6.9 vs. 12.2 ± 4.6 mmHg; p = 0.93). In the Kolar study, ETCO2 specificity progressively decreased from 100% at 20 min to 98%, 60% and 50% at 15, 10, and 0 min respectively [31]. Other studies [32–34] confirmed a low accuracy of initial ETCO2 in predicting ROSC, especially as far as specificity was concerned. In patients with asphyxial arrest this is likely because their initial ETCO2 is high, reflecting pre-arrest hypercapnia rather than optimal tissue perfusion [35].

In general, ETCO2 values tend to decrease during CPR in patients in whom resuscitation is unsuccessful, while they tend to increase in those who achieve ROSC, probably reflecting a progressive improvement in tissue perfusion and venous return [30,33]. For this reason, ETCO2 trends might be more appropriate than point values for predicting ROSC during CPR. However, evidence on this is still limited [36].

Most of the studies on predictive value of ETCO2 have important limitations, including lack of power analysis or blinding, uncontrolled ventilation during CPR, and inconsistent or undefined timings of ETCO2 measurement [37,38]. Additional well-designed studies are needed to better identify the optimal measurement timings and cut-off values for prognostication using ETCO2. The 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) [39] on ALS recommends against using ETCO2 cut-off values alone as a mortality predictor or for the decision to stop a resuscitation attempt.

A specific prognostic indication for ETCO2 measurement during CPR is the identification of patients with refractory cardiac arrest who are eligible for emergency extracorporeal life support. When resuscitation lasts longer than 20 min the chances of achieving a meaningful survival with conventional CPR are very low [40,41] and extracorporeal cardiopulmonary resuscitation (ECPR), with veno-arterial extracorporeal membrane oxygenation (VA-ECMO), can be used as a rescue therapy. However, the potential benefit of ECPR should be balanced against the risk of futility, post-anoxic brain damage [23] and high costs [40,41], so that selecting patients who will benefit most from ECPR is essential. The 2009 Guidelines on indications for the use of extracorporeal life support in refractory cardiac arrest issued by French medical Societies [42] recommended ETCO2 above 10 mmHg as a criterion for considering ECPR in patients with refractory cardiac arrest with no-flow duration ≤ 5 min and low-flow duration ≤ 100 min. However, two recent systematic reviews which investigated predictors of survival after ECPR in refractory OHCA [43] or IHCA [44] did not find evidence supporting the use of ETCO2 in this context.

Another specific prognostic indication of ETCO2 may be prediction of defibrillation success. A recent retrospective study on 62 patients with OHCA from ventricular fibrillation [45] showed that none of them could be successfully defibrillated when ETCO2 in the minute preceding the shock was < 7 mmHg, while defibrillation was 100% successful in patients whose ETCO2 in the minute preceding the shock was > 45 mmHg. However, sensitivities for these signs were very low (5% and 7%, respectively). These preliminary data will need confirmation from further studies.

Confounding factors

When interpreting ETCO2 values during CPR a series of confounding factors need to be taken into account. As mentioned above, in patients with a respiratory cause of arrest, ETCO2 may initially be high [35,46] as a result of hypercapnia and may therefore not reflect cardiac output generated by CPR.

Conversely, hyperventilation decreases ETCO2 levels during CPR. In a pig model of cardiac arrest Gazmuri et al. [47] demonstrated that increasing either respiratory rate from the recommended value of 10 breaths·min⁻¹ to 33 breaths·min⁻¹, or tidal volume from 6 ml·kg⁻¹ to 18 ml·kg⁻¹ during CPR had similar effects on the mean ETCO2, which decreased from 43 ± 8 to 20 ± 1 and 20 ± 6 mmHg, respectively (Fig. 3). When both ventilation rate and tidal volume were increased
from baseline to 33 breaths/min \(^{-1}\) and 18 ml kg\(^{-1}\) respectively, ETCO\(_2\) decreased further to 14 ± 2 mmHg but the rate of decrease was slower. Interestingly, no differences were observed in terms of arterial, coronary, and cerebral perfusion pressures across the groups assigned to the four different ventilation patterns.

Both ETCO\(_2\) values and their clinical significance may be affected by drugs used during resuscitation. In experimental CPR the administration of adrenaline is followed by a rapid decrease of ETCO\(_2\) despite a parallel increase in coronary and cerebral perfusion pressure [2,48,49]. The presumed mechanism is a reduced CO\(_2\) elimination through the lungs due to an adrenaline-induced constriction of the pulmonary vasculature with increased shunting and ventilation-perfusion mismatch [2]. However, an actual reduction of tissue perfusion due to the negative effects of adrenaline on microcirculation mediated by its \(\alpha\)-agonist action cannot be excluded [50]. In a canine model of cardiac arrest Martin et al. [49] showed that the positive correlation between coronary perfusion pressure and ETCO\(_2\) was lost two minutes after the administration of adrenaline (from \(r = 0.97, p = 0.0005\) to \(r = 0.35, p = 0.24\)). Therefore, low or decreasing ETCO\(_2\) levels during CPR may not necessarily indicate poor prognosis when measured shortly after an adrenaline bolus. In a clinical observational study from Callaham et al. [51] ETCO\(_2\) decreased in 25/64 (39%) cardiac arrest patients four minutes after adrenaline was administered. However, presence of an ETCO\(_2\) decrease after an adrenaline administration was most often associated with ROSC, while absence of an ETCO\(_2\) decrease had a 92% positive predictive value for no ROSC.

The administration of sodium bicarbonate during CPR transiently elevates ETCO\(_2\) because buffering of H\(^+\) with bicarbonate produces CO\(_2\). In an animal model of arrest, intravenous administration of 0.2 mmol \cdot kg\(^{-1}\) of sodium bicarbonate during resuscitation was followed by a mean ETCO\(_2\) increase of 6.4 ± 0.5 mmHg [52]. Rescuers should be aware of this, in order not to misinterpret an ETCO\(_2\) increase following bicarbonate administration as patient having ROSC. When compared with the transient ETCO\(_2\) increase after bicarbonate bolus, the ETCO\(_2\) rise following ROSC is much higher and steady [24].

**Conclusion**

Measurement of ETCO\(_2\) is currently the only noninvasive clinical tool for estimating organ perfusion during CPR. During experimental CPR, ETCO\(_2\) has shown a significant positive correlation with cardiac index and with coronary and cerebral perfusion pressures. In observational studies on pre-hospital cardiac arrest, ETCO\(_2\) levels below 10 mmHg after 20 min of ALS were highly predictive of pre-hospital mortality. However, accuracy of ETCO\(_2\) as a predictor of ROSC is lower when it is measured earlier during cardiac arrest. In addition, the aetiology of cardiac arrest, changes in ventilation patterns, and the effects of adrenaline or sodium bicarbonate may significantly affect ETCO\(_2\) levels during resuscitation.

ETCO\(_2\) monitoring can be used to confirm intubation during cardiac arrest. While detection of ETCO\(_2\) in the exhaled air is the most specific sign confirming placement of endotracheal tube, absence of detectable ETCO\(_2\) does not always indicate a failed intubation. Furthermore, ETCO\(_2\) cannot discriminate between endotracheal and endobronchial tube placement, and clinical confirmation with chest auscultation is recommended. Finally, an abrupt ETCO\(_2\) rise during CPR suggests that ROSC has occurred. However, in order to achieve a sufficient specificity, detection of ROSC using ETCO\(_2\) rise may require several minutes, which limits its clinical applicability. Current guidelines recommend against using ETCO\(_2\) levels as the only criterion for decision making during cardiac arrest.

**Conflict of interest statement**

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship but are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all of us.

We confirm that we have given due consideration to the protection of intellectual property associated with this work and that there are no impediments to publication, including the timing of publication, with respect to intellectual property. In so doing we confirm that we have followed the regulations of our institutions concerning intellectual property.

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