Capnography during cardiac arrest

Claudio Sandroni, Paolo De Santis and Sonia D'Arrigo

Istituto Anestesiologia e Rianimazione Università Cattolica del Sacro Cuore - Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS


References: 52

Corresponding Author:

Dr. Claudio Sandroni

Istituto Anestesiologia e Rianimazione Università Cattolica del Sacro Cuore
Fondazione Policlinico Universitario "Agostino Gemelli" IRCCS
Largo Francesco Vito, 1 – 00168 Rome, Italy
email: claudio.sandroni@policlinicogemelli.it

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 ETCO$_2$ levels and its clinical significance. While identifying ETCO$_2$ as a useful monitoring tool during resuscitation, current guidelines for advanced life support recommend against using ETCO$_2$ values in isolation for decision making in cardiac arrest management.

Keywords: Cardiac arrest; End tidal carbon dioxide; Capnography; Prognosis; Ventilation; Advanced cardiac life support; Review.

Introduction

End-tidal carbon dioxide (ETCO$_2$) is the partial pressure of carbon dioxide (PCO$_2$) in the exhaled air measured at the end of expiration. CO$_2$ 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 ETCO$_2$ therefore include CO$_2$ production, cardiac output (CO), lung perfusion and alveolar ventilation$^1$. Capnography represents a continuous, non-invasive measurement of PCO$_2$ in the exhaled air during the breathing cycle. The correspondent waveform is called a capnogram (Fig. 1).

In the typical capnogram ETCO$_2$ is the value recorded at the end of the plateau phase and it is the one which better reflects the alveolar PCO$_2$. Normally, ETCO$_2$ is around 5 mmHg lower than PCO$_2$ in the arterial blood (PaCO$_2$). 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$^2$.

ETCO$_2$ 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 correlates well with CI (r = .79 ; p < .001)⁷ coronary perfusion pressure (r = .78 ; p < .01)⁸ and cerebral blood flow (r = .64 ; p = .01)⁹. In clinical studies a direct correlation between ETCO₂ and CO or tissue perfusion has not been demonstrated yet, but it is supported by indirect evidence of the association between ETCO₂ and CPR quality. In a multicenter observational study including 583 in-hospital (IHCA) and out-of-hospital (OHCA) arrests, Sheak et al.¹⁰ showed that for every 10 mm increase in chest compression depth, ETCO₂ increased by 1.4 mmHg (p < .001). In a larger prospective study by Murphy et al.¹¹ on 1217 OHCAs, a 10 mm increase in chest compression depth was associated with a 4.0% increase in ETCO₂ (p < .0001), a 10/minute increase in chest compression rate with a 1.7% increase in ETCO₂ (p = .02), and a 10 breath/minute increase in ventilation rate with a 17.4% decrease in ETCO₂ (p < .0001). In 2013, a consensus document from the American Heart Association¹² recommended ETCO₂ as the primary physiological metric during CPR when neither an arterial nor a central venous catheter is in place and suggested titrating CPR performance to a goal ETCO₂ of >20 mmHg. The European Resuscitation Council (ERC) 2015 guidelines¹³ on advanced life support (ALS) suggest using waveform capnography during cardiac arrest to assess the quality of CPR but did not provide a specific ETCO₂ target for resuscitation.

Another important quality target of CPR is avoiding hyperventilation. Although ALS guidelines recommend ventilating patients at 10 breaths · min⁻¹ during CPR, ventilation up to 30 breaths · min⁻¹ by rescue
personnel in OHCA has been observed\textsuperscript{14}. Hyperventilation during ALS is more common in inexperienced or uncertified providers\textsuperscript{15} and has potential unfavourable haemodynamic effects\textsuperscript{16}. Waveform capnography allows monitoring of ventilation rate during CPR, however interference from chest compression artefacts may degrade ventilation detection and cause false hyperventilation alarms\textsuperscript{17}. The use of automated analysis of the capnogram can reduce measurement error of the ventilation rate to 1.8 breaths ∙ min\textsuperscript{-1} and accuracy of ventilation alarms to >99\%\textsuperscript{18}.

**ETCO\textsubscript{2} to confirm endotracheal tube placement during CPR**

Performing a rapid and successful endotracheal intubation during resuscitation from cardiac arrest is important. Detection of CO\textsubscript{2} in exhaled air using waveform capnography is the most specific method for confirming endotracheal tube placement.

A study\textsuperscript{19} from Grmec et al. on 246 OHCAs who underwent prehospital intubation showed that capnography had 100\%(97-100\%) specificity and 100\%(98-100\%) sensitivity for detecting correct endotracheal tube placement. In a study\textsuperscript{20} on 81 OHCAs who were intubated on arrival to the emergency department, a detectable ETCO\textsubscript{2} at the fifth breath after the intubation attempt measured using capnogram was also 100\%(72-100\%) specific. However, ETCO\textsubscript{2} was not detectable in 26/72 correctly positioned tubes (64\%(52-75\%) sensitivity). The threshold for ETCO\textsubscript{2} detection was 2 mmHg in that study. In a study from Tanigawa et al.\textsuperscript{21} in 65 OHCAs who were intubated after a mean of 34 minutes from arrest, ETCO\textsubscript{2} was undetectable in 5/5 oesophageal intubations (specificity 100\%(55-100\%), but it could not be measured in 26 tracheal intubations (sensitivity 57\%(43-69\%), although a small ETCO\textsubscript{2} waveform was observed in seven of these cases. Similar results were shown in a subsequent crossover study\textsuperscript{22} from the same authors where 48 cardiac arrest patients were randomly assigned to ETCO\textsubscript{2} or to oesophageal detector device to confirm intubation.

In summary, in cardiac arrest patients the presence of a detectable ETCO\textsubscript{2} on waveform capnography accurately confirms endotracheal tube placement, while its absence does not completely rule out a successful intubation. One potential cause for this may be an absent or very low venous return because of prolonged resuscitation. In one to the studies cited above,\textsuperscript{21} patients with undetectable ETCO\textsubscript{2} had longer
cardiac arrest duration at the time of measurement than those with detectable ETCO\textsubscript{2} although the difference was not significant (37.6 ±13 min vs. 32.6 ±13 min, respectively).

In the four studies mentioned above the predictive value of an absent ETCO\textsubscript{2} waveform for endotracheal tube misplacement was only 27\% (19–37\%). However, since an unrecognized oesophageal intubation is potentially fatal, removing the tube in absence of a detectable ETCO\textsubscript{2} on waveform capnography appears to be the most reasonable strategy.

Another caveat for ETCO\textsubscript{2} 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\textsuperscript{13} recommend using waveform capnography in addition to clinical assessment to confirm and continuously monitor endotracheal tube placement.

**ETCO\textsubscript{2} to detect ROSC**

ROSC is associated with a significant increase of ETCO\textsubscript{2} (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\textsuperscript{24}. ETCO\textsubscript{2} 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\textsuperscript{19,25,26}. Therefore, when detecting occurrence of ROSC, a high level of specificity (i.e., low rates of false positive results) are required\textsuperscript{27}.

In a retrospective case control study conducted on 108 OHCAs, Pokorna et al.\textsuperscript{28} showed that a sudden increase of ETCO\textsubscript{2} 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.\textsuperscript{29} showed that an ETCO\textsubscript{2} 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 ETCO\textsubscript{2} increase and the subsequent ROSC, however, was 12 min, much longer than the 2-minute interval between two subsequent pulse checks as per the ALS algorithm.
The ERC ALS 2015 guidelines\textsuperscript{1} indicate that ETCO\textsubscript{2} can be a marker of ROSC during CPR and suggest checking electrocardiogram for presence of an organized rhythm when a rise in ETCO\textsubscript{2} occurs. However, no specific ETCO\textsubscript{2} threshold for interrupting CPR could be recommended.

**ETCO\textsubscript{2} to predict survival from cardiac arrest**

Since ETCO\textsubscript{2} 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.\textsuperscript{30} investigated on the association between ETCO\textsubscript{2} measured after 20 minutes 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 ETCO\textsubscript{2}≤10 mmHg after 20 minutes of ALS survived to hospital admission, while all patients with ETCO\textsubscript{2}>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.\textsuperscript{31} on 737 OHCAs from all rhythms using a >14.3 mmHg threshold at 20 minutes. The study also measured ETCO\textsubscript{2} at 0, 10, and 15 minutes and showed that no patient with <10 mmHg ETCO\textsubscript{2} survived at any time.

ETCO\textsubscript{2} 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.\textsuperscript{30} mentioned above, initial ETCO\textsubscript{2} values did not differ between survivors and non-survivors (12.3 ± 6.9 vs. 12.2 ± 4.6 mmHg; \(p = .93\)). In the Kolar study, ETCO\textsubscript{2} specificity progressively decreased from 100% at 20 minutes to 98%, 60% and 50% at 15, 10, and 0 minutes respectively. Other studies\textsuperscript{32-34} confirmed a low accuracy of initial ETCO\textsubscript{2} in predicting ROSC, especially as far as specificity was concerned. In patients with asphyxial arrest this is likely because their initial ETCO\textsubscript{2} is high, reflecting pre-arrest hypercapnia rather than optimal tissue perfusion\textsuperscript{35}.

In general, ETCO\textsubscript{2} 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\textsuperscript{30, 31}. For this reason, ETCO\textsubscript{2} trends might be more appropriate than point values for predicting ROSC during CPR. However, evidence on this is still limited\textsuperscript{36}.

Most of the studies on predictive value of ETCO\textsubscript{2} have important limitations, including lack of power analysis or blinding, uncontrolled ventilation during CPR, and inconsistent or undefined timings of ETCO\textsubscript{2} measurement\textsuperscript{37, 38}. Additional well-designed studies are needed to better identify the optimal measurement timings and cut-off values for prognostication using ETCO\textsubscript{2}. The 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR)\textsuperscript{39} on ALS recommends against using ETCO\textsubscript{2} cut-off values alone as a mortality predictor or for the decision to stop a resuscitation attempt.

A specific prognostic indication for ETCO\textsubscript{2} 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\textsuperscript{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\textsuperscript{23} and high costs\textsuperscript{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\textsuperscript{42} recommended ETCO\textsubscript{2} above 10 mmHg as a criterion for considering ECPR in patients with refractory cardiac arrest with no-flow duration ≤5 minutes and low-flow duration ≤100 minutes. However, two recent systematic reviews which investigated predictors of survival after ECPR in refractory OHCA\textsuperscript{43} or IHCA\textsuperscript{44} did not find evidence supporting the use of ETCO\textsubscript{2} in this context.

Another specific prognostic indication of ETCO\textsubscript{2} may be prediction of defibrillation success. A recent retrospective study on 62 patients with OHCA from ventricular fibrillation\textsuperscript{45} showed that none of them could be successfully defibbrillated when ETCO\textsubscript{2} in the minute preceding the shock was <7 mmHg, while defibrillation was 100% successful in patients whose ETCO\textsubscript{2} 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 ETCO$_2$ 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, ETCO$_2$ may initially be high\textsuperscript{35,46} as a result of hypercapnia and may therefore not reflect cardiac output generated by CPR.

Conversely, hyperventilation decreases ETCO$_2$ levels during CPR. In a pig model of cardiac arrest Gazmuri et al.\textsuperscript{47} demonstrated that increasing either respiratory rate from the recommended value of 10 breaths $\cdot$ min$^{-1}$ to 33 breaths $\cdot$ min$^{-1}$, or tidal volume from 6 ml $\cdot$ kg$^{-1}$ to 18 ml $\cdot$ kg$^{-1}$ during CPR had similar effects on the mean ETCO$_2$, which decreased from 43 $\pm$ 8 to 20 $\pm$ 1 and 20 $\pm$ 6 mmHg, respectively (Fig. 3). When both ventilation rate and tidal volume were increased from baseline to 33 breaths $\cdot$ min$^{-1}$ and 18 ml $\cdot$ kg$^{-1}$ respectively, ETCO$_2$ decreased further to 14 $\pm$ 2 mmHg but the rate of decrease was slower. Interestingly, no differences were observed in terms of aortic, 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\textsuperscript{3,48,49}. 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\textsuperscript{2}. However, an actual reduction of tissue perfusion due to the negative effects of adrenaline on microcirculation mediated by its $\alpha$-1 agonist action cannot be excluded\textsuperscript{50}. In a canine model of cardiac arrest Martin et al.\textsuperscript{49} showed that the positive correlation between coronary perfusion pressure and ETCO$_2$ was lost two minutes after the administration of adrenaline (from $r = .97$, $p = .0005$ to $r = .35$, $p = .24$). 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.,\textsuperscript{51} ETCO$_2$ decreased in 25/64 (39%) cardiac arrest patients.
four minutes after adrenaline was administered. However, presence of an ETCO₂ decrease after an adrenaline administration was most often associated with ROSC, while absence of an ETCO₂ decrease had a 92% positive predictive value for no ROSC.

The administration of sodium bicarbonate during CPR transiently elevates ETCO₂ because buffering of H⁺ with bicarbonate produces CO₂. In an animal model of arrest, intravenous administration of 0.2 mmol·kg⁻¹ of sodium bicarbonate during resuscitation was followed by a mean ETCO₂ increase of 6.4 ± 0.5 mmHg. Rescuers should be aware of this, in order not to misinterpret an ETCO₂ rise following bicarbonate administration as patient having ROSC. When compared with the transient ETCO₂ increase after bicarbonate bolus, the ETCO₂ rise following ROSC is much higher and steady.

Conclusion

Measurement of ETCO₂ is currently the only noninvasive clinical tool for estimating organ perfusion during CPR. During experimental CPR, ETCO₂ has shown a significant positive correlation with cardiac index and with coronary and cerebral perfusion pressures. In observational studies on pre-hospital cardiac arrest, ETCO₂ levels below 10 mmHg after 20 minutes of ALS were highly predictive of pre-hospital mortality.

However, accuracy of ETCO₂ 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 ETCO₂ levels during resuscitation.

ETCO₂ monitoring can be used to confirm intubation during cardiac arrest. While detection of ETCO₂ in the exhaled air is the most specific sign confirming placement of endotracheal tube, absence of detectable ETCO₂ does not always indicate a failed intubation. Furthermore, ETCO₂ cannot discriminate between endotracheal and endobronchial tube placement, and clinical confirmation with chest auscultation is recommended. Finally, an abrupt ETCO₂ rise during CPR suggests that ROSC has occurred. However, in order to achieve a sufficient specificity, detection of ROSC using ETCO₂ rise may require several minutes, which limits its clinical applicability. Current guidelines recommend against using ETCO₂ levels as the only criterion for decision making during cardiac arrest.
Acknowledgments and funding

None.

CONFLICT OF INTEREST STATEMENT

Article: “Capnography during cardiac arrest” by Claudio Sandroni, Paolo De Santis, Sonia D’Arrigo

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.

We understand that the Corresponding Author is the sole contact for the Editorial process (including Editorial Manager and direct communications with the office). He is responsible for communicating with the other authors about progress, submissions of revisions and final approval of proofs. We confirm that we have provided a current, correct email address which is accessible by the Corresponding Author.

Signed by all authors as follows:

Claudio Sandroni 18/07/2018

Paolo De Santis 17/07/2018

Sonia D’Arrigo 18/07/2018

Reproduced from Gazmuri R et al. Resuscitation 2012; 83:259-64, with permission.
References


47. Gazmuri R J, Ayoub I M, Radhakrishnan J, Motl J, Upadhyaya M P. Clinically plausible hyperventilation does not exert adverse hemodynamic effects during CPR but markedly reduces end-tidal PCO(2). Resuscitation 2012; 83:259-64.


Legends to figures


Figure 2. Relationship between ETCO₂ and cardiac index before cardiac arrest, during CPR and after restoration of spontaneous circulation.

CI = Cardiac Index. CPR = Cardiopulmonary Resuscitation. VF = Ventricular Fibrillation.


Figure 3. ETCO₂ plotted as a function of the minute volume delivered during CPR with four different ventilation patterns: 10 breaths • min⁻¹ and 6 ml•kg⁻¹ tidal volume, 10 breaths • min⁻¹ and 18 ml•kg⁻¹, 33 breaths • min⁻¹ and 6 ml•kg⁻¹ and 33 breaths • min⁻¹ and 18 ml•kg⁻¹ (see legend). Each data point represents the ETCO₂ of one experimental subject obtained by averaging the values at minutes 2, 4, 6, and 8. The regression line is based on an inverse first order polynomial function and is shown with its 95% confidence intervals.

Manuscript “Capnography during cardiac arrest” by Claudio Sandroni, Paolo De Santis and Sonia D’Arrigo
Fig. 1

PCO₂ (mmHg) vs. Time

A B C D E

Exp. Insp.
Figure 2

Figure 3
