Resuscitation 132 (2018) 73–77

Contents lists available at ScienceDirect

Resuscitation

journal homepage: www.elsevier.com/locate/resuscitation

Review

Capnography during cardiac arrest

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ARTICLE INFO

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

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 ($ETCO_2$) 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 $ETCO_2$ levels in patients with ROSC are higher than those in patients with no ROSC. In prolonged out of hospital cardiac arrest, $ETCO_2$ 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 $ETCO_2$ during CPR suggests that ROSC has occurred. Finally, detection of CO_2 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 arrestmanagement.

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. $ETCO_2$ 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 $ETCO_2$ changes paralleled those of cardiac index (CI) during cardiac arrest and subsequent CPR (Fig. 2). When ventricular fibrillation was induced, $ETCO_2$ dropped to zero along with CI. During CPR, $ETCO_2$ was about 25% of pre-arrest values, as was CI generated by CPR. After successful defibrillation and return of spontaneous circulation (ROSC), $ETCO_2$ increased rapidly, exceeding its pre-arrest values. This $ETCO_2$ "overshoot" did not correspond to a proportional increase of CI, and it could be interpreted as a CO_2 washout from tissues that had been poorly perfused during cardiac arrest.

Experimental studies demonstrated that during CPR $ETCO_2$

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https://doi.org/10.1016/j.resuscitation.2018.08.018
Received 18 July 2018; Received in revised form 13 August 2018; Accepted 20 August 2018

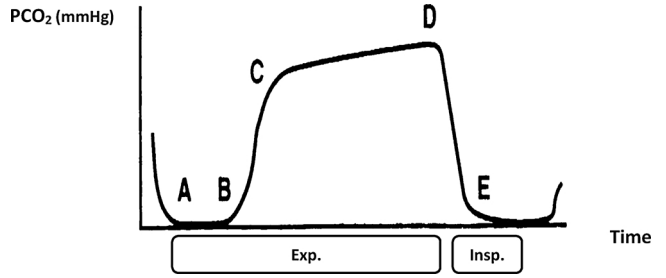

Fig. 1. Normal capnogram. A: expiration begins. A – B (phase I): consists of anatomical dead space, where CO_2 content is negligible. B – C (phase II, expiratory upstroke): rapid rise in PCO_2, the breath reaches upper airway from alveoli. C – D (phase III, alveolar plateau): uniform levels of CO_2 in the airway. The value recorded at the end of this plateau represents $ETCO_2$. D: inspiration begins. D – E (phase IV, inspiratory downstroke): CO_2 clearance. E: inspiration ends. PCO_2 = partial pressure of carbon dioxide. Exp. = Expiration. Insp. = Inspiration.

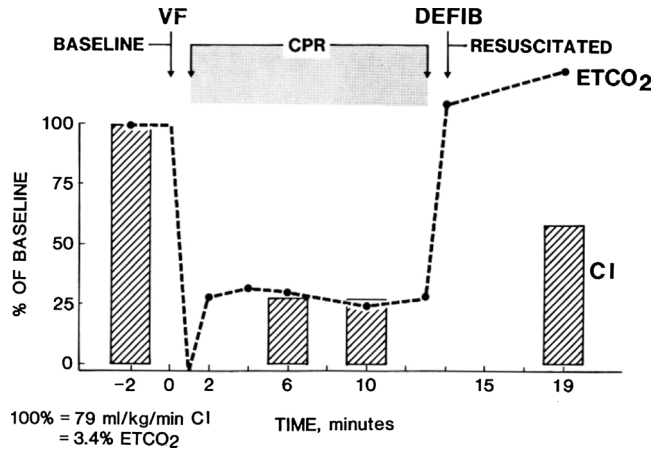

Fig. 2. Relationship between $ETCO_2$ and cardiac index before cardiac arrest, during CPR and after restoration of spontaneous circulation. CI = Cardiac Index. CPR = Cardiopulmonary Resuscitation. VF = Ventricular Fibrillation. Reproduced from Gudipati et al. Circulation 1988; 77:234-9, with permission.

correlates well with CI (r = 0.79 ; $p < 0.001$) [7] coronary perfusion pressure (r = 0.78; $p < 0.01$) [8] and cerebral blood flow (r = 0.64; $p = 0.01$) [9]. In clinical studies a direct correlation between $ETCO_2$ and CO or tissue perfusion has not been demonstrated yet, but it is supported by indirect evidence of the association between $ETCO_2$ 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, $ETCO_2$ increased by 1.4 mmHg ($p < 0.001$). 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 $ETCO_2$ ($p < 0.0001$), a 10/minute increase in chest compression rate with a 1.7% increase in $ETCO_2$ ($p = 0.02$), and a 10 breath/minute increase in ventilation rate with a 17.4% decrease in $ETCO_2$ ($p < 0.0001$). In 2013, a consensus document from the American Heart Association [12] recommended $ETCO_2$ 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 $ETCO_2$ of > 20 mmHg. The European Resuscitation Council (ERC) 2015 guidelines [13] on advanced life support (ALS) suggest using waveform capnography during cardiac arrest to assess the quality of CPR but did not provide a specific $ETCO_2$ 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 [14]. Hyperventilation during ALS is more common in inexperienced or uncertified providers [15] and has potential unfavourable haemodynamic effects [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 [17]. The use of automated analysis of the capnogram can reduce measurement error of the ventilation rate to 1.8 breaths·min^{-1} and accuracy of ventilation alarms to > 99% [18].

$ETCO_2$ to confirm endotracheal tube placement during CPR

Performing a rapid and successful endotracheal intubation during resuscitation from cardiac arrest is important. Detection of CO_2 in exhaled air using waveform capnography is the most specific method for confirming endotracheal tube placement.

A study [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 [20] on 81 OHCAs who were intubated on arrival to the emergency department, a detectable $ETCO_2$ at the fifth breath after the intubation attempt measured using capnogram was also 100[72–100]% specific. However, $ETCO_2$ was not detectable in 26/72 correctly positioned tubes (64[52–75]% sensitivity). The threshold for $ETCO_2$ detection was 2 mmHg in that study. In a study from Tanigawa et al. [21] in 65 OHCAs who were intubated after a mean of 34 min from arrest, $ETCO_2$ 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 $ETCO_2$ waveform was observed in seven of these cases. Similar results were shown in a subsequent crossover study [22] from the same authors where 48 cardiac arrest patients were randomly assigned to $ETCO_2$ or to oesophageal detector device to confirm intubation.

In summary, in cardiac arrest patients the presence of a detectable $ETCO_2$ 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, [21] patients with undetectable $ETCO_2$ had longer cardiac arrest duration at the time of measurement than those with detectable $ETCO_2$ 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 $ETCO_2$ 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 $ETCO_2$ on waveform capnography appears to be the most reasonable strategy.

Another caveat for $ETCO_2$ 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 [13] recommend using waveform capnography in addition to clinical assessment to confirm and continuously monitor endotracheal tube placement.

$ETCO_2$ to detect ROSC

ROSC is associated with a significant increase of $ETCO_2$ (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 [24]. $ETCO_2$ 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 [19,25,26]. Therefore, when detecting occurrence of ROSC, a high level of specificity (i.e., low rates of false positive results) are required

[27].

In a retrospective case control study conducted on 108 OHCAs, Pokorna et al. [28] showed that a sudden increase of $ETCO_2$ 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. [29] showed that an $ETCO_2$ 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 $ETCO_2$ 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[1] indicate that $ETCO_2$ can be a marker of ROSC during CPR and suggest checking electrocardiogram for presence of an organized rhythm when a rise in $ETCO_2$ occurs. However, no specific $ETCO_2$ threshold for interrupting CPR could be recommended.

$ETCO_2$ to predict survival from cardiac arrest

Since $ETCO_2$ 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. [30] investigated on the association between $ETCO_2$ 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 $ETCO_2$ ≤10 mmHg after 20 min of ALS survived to hospital admission, while all patients with $ETCO_2$ > 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. [31] on 737 OHCAs from all rhythms using a > 14.3 mmHg threshold at 20 min. The study also measured $ETCO_2$ at 0, 10, and 15 min and showed that no patient with < 10 mmHg $ETCO_2$ survived at any time.

$ETCO_2$ 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. [30] mentioned above, initial $ETCO_2$ 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, $ETCO_2$ 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 $ETCO_2$ in predicting ROSC, especially as far as specificity was concerned. In patients with asphyxial arrest this is likely because their initial $ETCO_2$ is high, reflecting pre-arrest hypercapnia rather than optimal tissue perfusion [35].

In general, $ETCO_2$ 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 [30,33]. For this reason, $ETCO_2$ 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 $ETCO_2$ have important limitations, including lack of power analysis or blinding, uncontrolled ventilation during CPR, and inconsistent or undefined timings of $ETCO_2$ measurement [37,38]. Additional well-designed studies are needed to better identify the optimal measurement timings and cut-off values for prognostication using $ETCO_2$. The 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations (CoSTR) [39] on ALS recommends against using $ETCO_2$ cut-off values alone as a mortality predictor or for the decision to stop a resuscitation attempt.

A specific prognostic indication for $ETCO_2$ 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 [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 $ETCO_2$ 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 $ETCO_2$ in this context.

Another specific prognostic indication of $ETCO_2$ 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 $ETCO_2$ in the minute preceding the shock was < 7 mmHg, while defibrillation was 100% successful in patients whose $ETCO_2$ 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 [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. [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 $ETCO_2$, which decreased from 43 ± 8 to 20 ± 1 and 20 ± 6 mmHg, respectively (Fig. 3). When both ventilation rate and tidal volume were increased

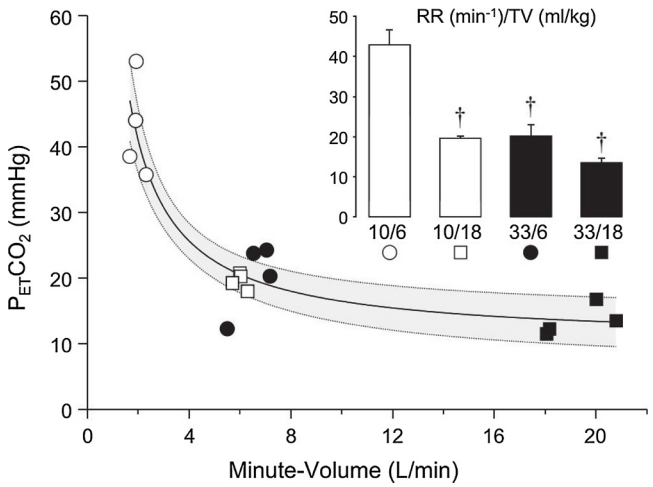

Fig. 3. $ETCO_2$ plotted as a function of the minute volume delivered during CPR with four different ventilation patterns: 10 breaths · min^{-1} and 6·ml·kg^{-1} tidal volume, 10 breaths · min^{-1} and 18 ml·kg^{-1}, 33 breaths · min^{-1} and 6 ml·kg^{-1} and 33 breaths · min^{-1} and 18 ml·kg^{-1} (see legend). Each data point represents the $ETCO_2$ 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.
Reproduced from Gazmuri R et al. Resuscitation 2012; 83:259-64, with permission.

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 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 [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 α-1 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 · 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 $ETCO_2$ rise 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.

Acknowledgment

None.

References

[1] Trillo G, von Planta M, Kette F. ETCO2 monitoring during low flow states: clinical aims and limits. Resuscitation 1994;27:1–8.
[2] Tang W, Weil MH, Gazmuri RJ, Sun S, Duggal C, Bisera J. Pulmonary ventilation/perfusion defects induced by epinephrine during cardiopulmonary resuscitation. Circulation 1991;84:2101–7.
[3] Sanders AB, Ewy GA, Taft TV. Prognostic and therapeutic importance of the aortic diastolic pressure in resuscitation from cardiac arrest. Crit Care Med 1984;12:871–3.
[4] Niemann JT, Criley JM, Rosborough JP, Niskanen RA, Alferness C. Predictive indices of successful cardiac resuscitation after prolonged arrest and experimental cardiopulmonary resuscitation. Ann Emerg Med 1985;14:521–8.
[5] Paradis NA, Martin GB, Rivers EP, Goetting MG, Appleton TJ, Feingold M, et al. Coronary perfusion pressure and the return of spontaneous circulation in human cardiopulmonary resuscitation. JAMA 1990;263:1106–13.
[6] Gudipati CV, Weil MH, Bisera J, Deshmukh HG, Rackow EC. Expired carbon dioxide: a noninvasive monitor of cardiopulmonary resuscitation. Circulation 1988;77:234–9.
[7] Weil MH, Bisera J, Trevino RP, Rackow EC. Cardiac output and end-tidal carbon dioxide. Crit Care Med 1985;13:907–9.
[8] Sanders AB, Atlas M, Ewy GA, Kern KB, Bragg S. Expired PCO2 as an index of coronary perfusion pressure. Am J Emerg Med 1985;3:147–9.
[9] Lewis LM, Stothert J, Standeven J, Chandel B, Kurtz M, Fortney J. Correlation of end-tidal CO2 to cerebral perfusion during CPR. Ann Emerg Med 1992;21:1131–4.
[10] Sheak KR, Wiebe DJ, Leary M, Babaeizadeh S, Yuen TC, Zive D, et al. Quantitative relationship between end-tidal carbon dioxide and CPR quality during both in-hospital and out-of-hospital cardiac arrest. Resuscitation 2015;89:149–54.
[11] Murphy RA, Bobrow BJ, Spaite DW, Hu C, McDannold R, Vadeboncoeur TF. Association between prehospital CPR quality and end-tidal carbon dioxide levels in out-of-hospital cardiac arrest. Prehosp Emerg Care 2016;20:369–77.
[12] Meaney PA, Bobrow BJ, Mancini ME, Christenson J, de Caen AR, Bhanji F, et al. Cardiopulmonary resuscitation quality: [corrected] improving cardiac resuscitation outcomes both inside and outside the hospital: a consensus statement from the American Heart Association. Circulation 2013;128:417–35.
[13] Soar J, Nolan JP, Bottiger BW, Perkins GD, Lott C, Carli P, et al. European Resuscitation Council Guidelines for resuscitation 2015: section 3. Adult advanced life support. Resuscitation 2015;95:100–47.
[14] Aufderheide TP, Lurie KG. Death by hyperventilation: a common and life-threatening problem during cardiopulmonary resuscitation. Crit Care Med 2004;32:S345–51.
[15] Park SO, Shin DH, Baek KJ, Hong DY, Kim EJ, Kim SC, et al. A clinical observational study analysing the factors associated with hyperventilation during actual cardiopulmonary resuscitation in the emergency department. Resuscitation 2013;84:298–303.
[16] Aufderheide TP, Sigurdsson G, Pirrallo RG, Yannopoulos D, McKnite S, von Briesen C, et al. Hyperventilation-induced hypotension during cardiopulmonary resuscitation. Circulation 2004;109:1960–5.
[17] Leturiondo M, Ruiz de Gauna S, Ruiz JM, Julio Gutierrez J, Leturiondo LA, Gonzalez-Otero DM, et al. Influence of chest compression artefact on capnogram-based ventilation detection during out-of-hospital cardiopulmonary resuscitation. Resuscitation 2018;124:63–8.
[18] Aramendi E, Elola A, Alonso E, Irusta U, Daya M, Russell JK, et al. Feasibility of the capnogram to monitor ventilation rate during cardiopulmonary resuscitation. Resuscitation 2017;110:162–8.
[19] Grmec S. Comparison of three different methods to confirm tracheal tube placement in emergency intubation. Intensive Care Med 2002;28:701–4.
[20] Takeda T, Tanigawa K, Tanaka H, Hayashi Y, Goto E, Tanaka K. The assessment of three methods to verify tracheal tube placement in the emergency setting. Resuscitation 2003;56:153–7.
[21] Tanigawa K, Takeda T, Goto E, Tanaka K. Accuracy and reliability of the self-inflating bulb to verify tracheal intubation in out-of-hospital cardiac arrest patients. Anesthesiology 2000;93:1432–6.
[22] Tanigawa K, Takeda T, Goto E, Tanaka K. The efficacy of esophageal detector

devices in verifying tracheal tube placement: a randomized cross-over study of out-of-hospital cardiac arrest patients. Anesth Analg 2001;92:375–8.
[23] Soar J, Callaway CW, Aibiki M, Bottiger BW, Brooks SC, Deakin CD, et al. Part 4: advanced life support: 2015 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Resuscitation 2015;95:e71–120.
[24] Garnett AR, Ornato JP, Gonzalez ER, Johnson EB. End-tidal carbon dioxide monitoring during cardiopulmonary resuscitation. JAMA 1987;257:512–5.
[25] Edelson DP, Abella BS, Kramer-Johansen J, Wik L, Myklebust H, Barry AM, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. Resuscitation 2006;71:137–45.
[26] Vaillancourt C, Everson-Stewart S, Christenson J, Andrusiek D, Powell J, Nichol G, et al. The impact of increased chest compression fraction on return of spontaneous circulation for out-of-hospital cardiac arrest patients not in ventricular fibrillation. Resuscitation 2011;82:1501–7.
[27] Sandroni C, Ristagno G. End-tidal CO2 to detect recovery of spontaneous circulation during cardiopulmonary resuscitation: we are not ready yet. Resuscitation 2016;104:A5–6.
[28] Pokorna M, Necas E, Kratochvil J, Skripsky R, Andrlik M, Franek O. A sudden increase in partial pressure end-tidal carbon dioxide (P(ET)CO(2)) at the moment of return of spontaneous circulation. J Emerg Med 2010;38:614–21.
[29] Lui CT, Poon KM, Tsui KL. Abrupt rise of end tidal carbon dioxide level was a specific but non-sensitive marker of return of spontaneous circulation in patient with out-of-hospital cardiac arrest. Resuscitation 2016;104:53–8.
[30] Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. N Engl J Med 1997;337:301–6.
[31] Kolar M, Krizmaric M, Klemen P, Grmec S. Partial pressure of end-tidal carbon dioxide successful predicts cardiopulmonary resuscitation in the field: a prospective observational study. Crit Care 2008;12:R115.
[32] Poon KM, Lui CT, Tsui KL. Prognostication of out-of-hospital cardiac arrest patients by 3-min end-tidal capnometry level in emergency department. Resuscitation 2016;102:80–4.
[33] Grmec S, Klemen P. Does the end-tidal carbon dioxide (EtCO2) concentration have prognostic value during out-of-hospital cardiac arrest? Eur J Emerg Med 2001;8:263–9.
[34] Cantineau JP, Merckx P, Lambert Y, Sorkine M, Bertrand C, Duvaldestin P. Effect of epinephrine on end-tidal carbon dioxide pressure during prehospital cardiopulmonary resuscitation. Am J Emerg Med 1994;12:267–70.
[35] Grmec S, Lah K, Tusek-Bunc K. Difference in end-tidal CO2 between asphyxia cardiac arrest and ventricular fibrillation/pulseless ventricular tachycardia cardiac arrest in the prehospital setting. Crit Care 2003;7:R139–44.
[36] Brinkrolf P, Borowski M, Metelmann C, Lukas RP, Pidde-Kullenberg L, Bohn A. Predicting ROSC in out-of-hospital cardiac arrest using expiratory carbon dioxide concentration: Is trend-detection instead of absolute threshold values the key? Resuscitation 2018;122:19–24.
[37] Paiva EF, Paxton JH, O'Neil BJ. The use of end-tidal carbon dioxide (ETCO2) measurement to guide management of cardiac arrest: a systematic review. Resuscitation 2018;123:1–7.
[38] Touma O, Davies M. The prognostic value of end tidal carbon dioxide during cardiac arrest: a systematic review. Resuscitation 2013;84:1470–9.
[39] Soar J, Callaway CW, Aibiki M, Bottiger BW, Brooks SC, Deakin CD, et al. Part 4: Advanced life support: 2015 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Resuscitation 2015;95:e71–120.
[40] Nolan JP, Sandroni C. In this patient in refractory cardiac arrest should I continue CPR for longer than 30 min and, if so, how? Intensive Care Med 2017;43:1501–3.
[41] Reynolds JC, Frisch A, Rittenberger JC, Callaway CW. Duration of resuscitation efforts and functional outcome after out-of-hospital cardiac arrest: when should we change to novel therapies? Circulation 2013;128:2488–94.
[42] Riou B. Guidelines for indications for the use of extracorporeal life support in refractory cardiac arrest. Ann Fr Anesth Reanim 2009;28:182–90.
[43] Debaty G, Babaz V, Durand M, Gaide-Chevronnay L, Fournel E, Blancher M, et al. Prognostic factors for extracorporeal cardiopulmonary resuscitation recipients following out-of-hospital refractory cardiac arrest. A systematic review and meta-analysis. Resuscitation 2017;112:1–10.
[44] D'Arrigo S, Cacciola S, Dennis M, Jung C, Kagawa E, Antonelli M, et al. Predictors of favourable outcome after in-hospital cardiac arrest treated with extracorporeal cardiopulmonary resuscitation: a systematic review and meta-analysis. Resuscitation 2017;121:62–70.
[45] Savastano S, Baldi E, Raimondi M, Palo A, Belliato M, Cacciatore E, et al. End-tidal carbon dioxide and defibrillation success in out-of-hospital cardiac arrest. Resuscitation 2017;121:71–5.
[46] Heradstveit BE, Sunde K, Sunde GA, Wentzel-Larsen T, Heltne JK. Factors complicating interpretation of capnography during advanced life support in cardiac arrest–a clinical retrospective study in 575 patients. Resuscitation 2012;83:813–8.
[47] Gazmuri RJ, Ayoub IM, Radhakrishnan J, Motl J, Upadhyaya MP. Clinically plausible hyperventilation does not exert adverse hemodynamic effects during CPR but markedly reduces end-tidal PCO(2). Resuscitation 2012;83:259–64.
[48] Hardig BM, Gotberg M, Rundgren M, Gotberg M, Zughaft D, Kopotic R, et al. Physiologic effect of repeated adrenaline (epinephrine) doses during cardiopulmonary resuscitation in the cath lab setting: a randomised porcine study. Resuscitation 2016;101:77–83.
[49] Martin GB, Gentile NT, Paradis NA, Moeggenberg J, Appleton TJ, Nowak RM. Effect of epinephrine on end-tidal carbon dioxide monitoring during CPR. Ann Emerg Med 1990;19:396–8.
[50] Ristagno G, Tang W, Huang L, Fymat A, Chang YT, Sun S, et al. Epinephrine reduces cerebral perfusion during cardiopulmonary resuscitation. Crit Care Med 2009;37:1408–15.
[51] Callaham M, Barton C, Matthay M. Effect of epinephrine on the ability of end-tidal carbon dioxide readings to predict initial resuscitation from cardiac arrest. Crit Care Med 1992;20:337–43.
[52] Okamoto H, Hoka S, Kawasaki T, Okuyama T, Takahashi S. Changes in end-tidal carbon dioxide tension following sodium bicarbonate administration: correlation with cardiac output and haemoglobin concentration. Acta Anaesthesiol Scand 1995;39:79–84.