Resuscitation 84 (2013) 1470–1479

Contents lists available at ScienceDirect

Resuscitation

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

Review article

The prognostic value of end tidal carbon dioxide during cardiac arrest: A systematic review☆

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ARTICLE INFO

Article history:
Received 10 June 2013
Received in revised form 3 July 2013
Accepted 9 July 2013

Keywords:
Cardiac arrest
End tidal carbon dioxide
Prognosis
$ETCO_2$

ABSTRACT

Introduction: Cardiac arrest is a common presentation to the emergency care system. The decision to terminate CPR is often challenging to heath care providers. An accurate, early predictor of the outcome of resuscitation is needed. The purpose of this systematic review is to evaluate the prognostic value of $ETCO_2$ during cardiac arrest and to explore whether $ETCO_2$ values could be utilised as a tool to predict the outcome of resuscitation.
Method: Literature search was performed using Medline and EMBASE databases to identify studies that evaluated the relationship between $ETCO_2$ during cardiac arrest and outcome. Studies were thoroughly evaluated and appraised. Summary of evidence and conclusions were drawn from this systematic literature review.
Results: 23 observational studies were included. The majority of studies showed that $ETCO_2$ values during CPR were significantly higher in patients who later developed ROSC compared to patients who did not. Several studies suggested that initial $ETCO_2$ value of more than 1.33 kPa is 100% sensitive for predicting survival making $ETCO_2$ value below 1.33 kPa a strong predictor of mortality. These studies however had several limitations and the 100% sensitivity for predicting survival was not consistent among all studies.
Conclusion: $ETCO_2$ values during CPR do correlate with the likelihood of ROSC and survival and therefore have prognostic value. Although certain $ETCO_2$ cut-off values appears to be a strong predictor of mortality, the utility of $ETCO_2$ cut-off values during CPR to accurately predict the outcome of resuscitation is not fully established. Therefore, $ETCO_2$ values cannot be used as a mortality predictor in isolation.

Contents

Abbreviations: $ETCO_2$, end tidal carbon dioxide; CPR, cardiopulmonary resuscitation; ROSC, return of spontaneous circulation; RCT, randomised controlled trial; IQR, interquartile range; ED, emergency department; kPa, kiloPascal; CI, confidence interval; EMS, emergency medical services; PEA, pulseless electrical activity; BP, blood pressure; PPV, positive predictive value; NPV, negative predictive value; OR, odds ratio; MAP, mean arterial pressure; VF, ventricular fibrillation; VT, ventricular tachycardia; SD, standard deviation.

☆ A Spanish translated version of the summary of this article appears as Appendix in the final online version at http://dx.doi.org/10.1016/j.resuscitation.2013.07.011.

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http://dx.doi.org/10.1016/j.resuscitation.2013.07.011

1. Introduction

Cardiac arrest is a common presentation to the emergency care system. There are approximately 50,000 treated cardiac arrests each year in the UK with overall survival rate of less than 4%.[1] The decision to terminate cardiopulmonary resuscitation (CPR) is often challenging to heath care providers mainly due to the lack of objective and clearly defined criteria identifying patients who are not going to survive. Clinicians make decisions to stop CPR based mainly on clinical judgement, but also taking into consideration multiple factors that influence survival chance including the patient pre-morbid physiological reserves, the circumstances of the cardiac arrest, the length of the resuscitation efforts, and various bedside investigations such as blood gas analysis, lactate levels and the results of echocardiography. An accurate, early predictor of the outcome of resuscitation effort is needed. Such a predictor will not only limit therapies and preserve resources in futile cases, but also direct resources and aggressive treatments to patients who are likely to survive. Such predictor unfortunately does not exist and decisions to discontinue resuscitation efforts are heavily dependent on subjective clinical assessment and judgement.

The utility of capnography during cardiac arrest has been the centre of multiple studies in recent years. Capnography involves continuous monitoring of the partial pressure of the end tidal carbon dioxide ($ETCO_2$). The technique was first described in 1958 in anaesthetic practice as a method of confirming the correct placement of the endo-tracheal tube.[2] The technology behind capnography has evolved and improved such as that it is currently widely available in anaesthesia, intensive care medicine, emergency medicine and pre-hospital care. Experimental and clinical studies demonstrated close correlation between $ETCO_2$ and cardiac output.[3,4] $ETCO_2$ has therefore been used to reflect the efficacy of chest compressions during CPR and as an early indicator of return of spontaneous circulation (ROSC).[5,6] The strongly demonstrated association between $ETCO_2$ and cardiac output (therefore the indirect association between $ETCO_2$ and both coronary perfusion pressure and cerebral perfusion pressure) led to the increasing interest among investigators to explore the possible link between $ETCO_2$ during cardio-pulmonary arrest and resuscitation outcome.

The purpose of this systematic review is to explore the possible prognostic value of $ETCO_2$ during cardiac arrest. In specific, the questions that this review aims to answer are:

1 Does $ETCO_2$ have prognostic value during cardiac arrest?
2 Can the possible prognostic value of $ETCO_2$ be used to facilitate decision making regarding the termination of CPR?

2. Literature search

The literature search was performed on 17th September 2012. Both Medline and EMBASE databases were searched using the advanced search tool of the NHS Evidence search interface (https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases). The search was limited to English language and Humans studies. In addition, the limit for journal articles and reviews was used for EMBASE. Appendix 1 summarises the search strategy. Following de-duplicating the results from both databases, the search strategy resulted in 289 papers. Secondary resources search included Cochrane Library of Systematic Reviews, BestBETs database, Database of Abstracts and Reviews of Effects (DARE) and ClinicalTrials.gov and this revealed no results of direct relevance to the topic. The National Institute for Health and Clinical Excellence (NICE) and The Scottish Intercollegiate Guidelines Network (SIGN) had no guidance on the topic. The American Heart Association, the Resuscitation Council UK, and the International Liaison Committee on Resuscitation (ILCOR) recommendations and guidelines were reviewed and cross-referencing was performed along with backwards hand search of references of relevant studies to ensure no additional relevant papers were missed. 23 studies included in this systematic review. A flow diagram summarising the search results is shown in Fig. 1.

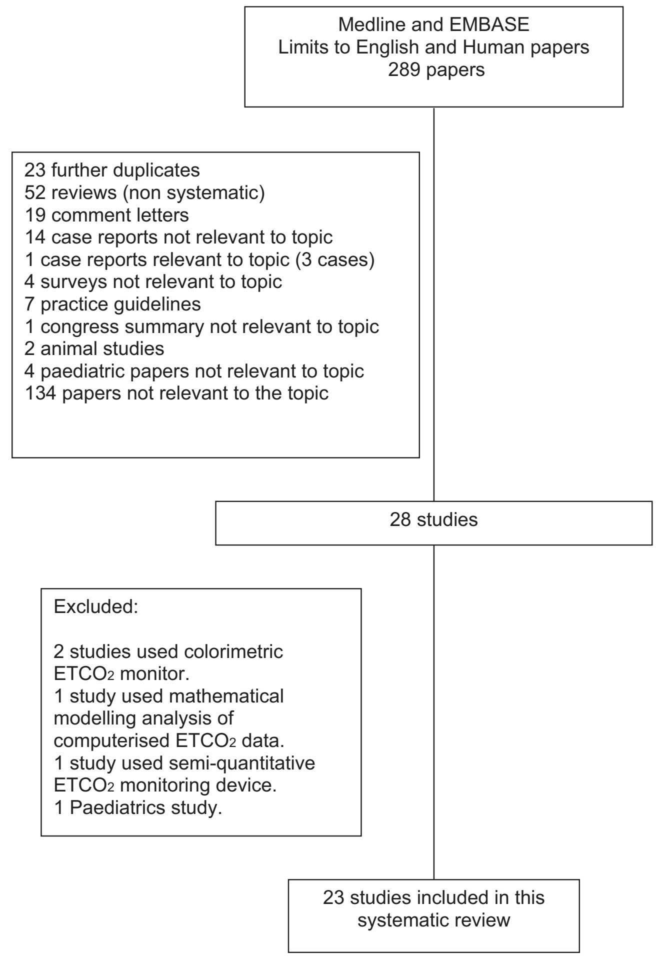

Fig. 1. Flow diagram of search results.

3. Overview of studies

Table 1 summarises the studies discussed in this systematic review. 22 studies were prospective observational and one study was a prospective randomised controlled trial (RCT). The value of the RCT was equivalent to an observational study for the purpose of this review as the main aim of this study was to investigate the difference in $ETCO_2$ values between standard CPR and active compression/decompression device, but it also compared $ETCO_2$ values between survivals and non-survivals. The studies varied in sample size ranging from 30 patients to 737 patients (median 127, IQR 64–264). The majority of the studies (16 out of 23) were conducted in the pre-hospital setting and in emergency medical services, five were conducted in the emergency department, one in an inpatient setting (including the ED), and 1 was combined inpatient and pre-hospital study.

Almost all studies looked into the association between $ETCO_2$ values and short term outcomes; either sustained ROSC, or ROSC associated with hospital admission. Although examining the relationship between $ETCO_2$ and longer term outcomes (such as survival to hospital discharge and functional outcome at discharge) would better inform clinical practice, it was impractical in a large

Table 1
Summary of studies.

Author, date, country, setting	Patients group	Study type	Outcomes	Key results
Kolar et al.[7] 2008 Slovenia Pre-hospital	737 adult non-traumatic cardiac arrest patients over nine year period with capnography monitoring.	Prospective observational study.	ROSC (defined as ROSC with hospitalisation). Survival to hospital discharge.	Both initial and final $ETCO_2$ were significantly higher in patients who had ROSC and survived to hospital discharge. For predicting ROSC: – Initial $ETCO_2 > 1.3$ kPa had 100% sensitivity and 50% specificity. – 20 min $ETCO_2 > 1.9$ kPa had 100% sensitivity and 100% specificity. For Predicting survival to hospital discharge: – Initial $ETCO_2 > 1.3$ kPa had 100% sensitivity and 34% specificity. In multivariate logistic analysis, initial and 20 min $ETCO_2$ were associated with improved ROSC (OR: 21.68, 95% CIs: 9.72–38.37, OR: 24.86, 95% CIs: 10.11–42.73 respectively)
Grmec et al.[8] 2003 Slovenia Pre-hospital	246 adult non-traumatic cardiac arrests patients over 3 year period. Initial post intubation $ETCO_2$ and final $ETCO_2$ (at ROSC or termination of CPR) were measured.	Prospective observational study.	ROSC (defined as ROSC with hospitalisation). Survival (defined as intensive care discharge).	Both initial and final $ETCO_2$ values were significantly higher in patients who had ROSC and patients who survived. All patients with ROSC and those who survived had initial $ETCO_2 > 1.33$ kPa. Using 1.33 kPa cut-off for predicting ROSC: Initial $ETCO_2$ had 100% sensitivity and 74% specificity. Final $ETCO_2$ had 100% sensitivity and 90% specificity. Using 1.33 kPa cut-off for predicting survival: Initial $ETCO_2$ had 100% sensitivity and 80% specificity. Final $ETCO_2$ had 100% sensitivity and 92% specificity. Using 2.13 cut-off for predicting survival: Initial $ETCO_2$ had 100% sensitivity and 94% specificity. Final $ETCO_2$ had 100% sensitivity and 95% specificity.
Grmec et al.[9] 2001 Slovenia Pre-hospital	139 adult non-traumatic cardiac arrests patients over 15 month period with capnography monitoring. $ETCO_2$ values were recorded every few minutes.	Prospective observational study.	ROSC (defined as palpable pulse for 10 min). Survival to hospital discharge.	Initial, final, maximal, minimal and average $ETCO_2$ values were all significantly higher for patients who had ROSC and for patients who survived to hospital discharge. All patients with ROSC had Initial $EtCO_2$ value of 1.33 kPa or greater. Using cut-off value of 1.33 kPa: Initial, final and average $ETCO_2$ were all 100% sensitive for predicting ROSC. (Specificity: 74.1%, 90.2% and 81.4% respectively)
Levine et al.[10] 1997 USA Emergency medical services	150 consecutive adult non-traumatic PEA cardiac arrests over 5 year period. 35 patients survived to hospital admission.	Prospective observational study.	Survival defined as survival to hospital admission.	No significant difference between initial $ETCO_2$ between survivors and non survivors but significant difference between $ETCO_2$ after 20 min of CPR. For predicting death, 20 min $ETCO_2 < 1.33$ kPa had 100% sensitivity, 100% specificity. (100% NPP and PPV) The upper 99 percent binomial confidence limit for the estimated survival was 3.9

Table 1 (*Continued*)

Author, date, country, setting	Patients group	Study type	Outcomes	Key results
Wayne at al.[11] 1995 USA Emergency medical services	90 consecutive adult non-traumatic PEA cardiac arrests over 3 year period. All patients resuscitated until ROSC or PEA became asystole (more than 20 min). 16 survived to hospital admission.	Prospective observational study.	ROSC (defined as survival to hospital admission).	No significant difference between initial $ETCO_2$ between survivors and non survivors. In patients who achieved ROSC, $ETCO_2$ just prior to ROSC was significantly higher compared to 20 min $ETCO_2$ for patients who never achieved ROSC. For predicting ROSC, 20 min $ETCO_2$ > 1.33 kPa had 100 sensitivity, 97.3% specificity (PPV: 88.9%, NPP: 100%)
Sanders et al.[12] 1989 USA in-patient	35 non-traumatic cardiac arrests (34 patients) over 1 year period in 2 centres. $ETCO_2$ was recorded every few minutes during CPR. The study included both in-hospital and out-of-hospital cardiac arrests. 9 patients had ROSC and 3 survived to hospital discharge.	Prospective observational study.	ROSC (defined as stable BP and departure of resuscitation team). Survival to hospital discharge.	Initial and average $ETCO_2$ were significantly higher for patients who had ROSC. Average $ETCO_2$ was significantly higher for patients who survived. The mean, maximum and minimum $ETCO_2$ were significant predictors of ROSC in a logistic regression analysis. All patients with ROSC had an average $ETCO_2$ > 1.33 For a cut-off value of 1.33, Average $ETCO_2$ was 100% sensitive, 77% specific (PPV 60%, NPV 100%) for predicting ROSC.
Callaham et al.[13] 1990 USA Emergency department	55 adult non-traumatic pre-hospital cardiac arrest patients treated in the ED of a single centre. Capnometry monitoring initiated in the emergency department. 14 patients had ROSC.	Prospective observational study.	ROSC (defined as palpable pulse for >10 min).	Initial $ETCO_2$ was significantly higher for patients who achieved ROSC. For predicting ROSC, initial $ETCO_2$ cut-off of 15 torr (approx 2 kPa) had 71% sensitivity, 98% specificity, 91% PPV, 91% NPP. 4 patients had initial $ETCO_2$ < 10 torr (1.33 kPa) and had ROSC. (2 in VT and 2 in asystole).
Callaham et al.[14] 1992 USA Emergency department	64 Adult non-traumatic pre-hospital cardiac arrest patients treated in the ED of a single centre over 41 months. The main aim of the study was to determine the effect of adrenaline administration on $ETCO_2$ values and therefore the effect it may have on $ETCO_2$ predictive ability. 15 patients had ROSC. No patients survived to hospital discharge.	Prospective observation study.	ROSC (defined as palpable pulse for >5 mins). Changes in $ETCO_2$ values after adrenaline administration.	For predicting ROSC, initial $ETCO_2$ (prior to adrenaline) cut-off of 10 torr (1.33 kPa) had 40% sensitivity, 87% specificity, 50% PPV, 82% NPP. Adrenaline may decrease $ETCO_2$ values, but does not change its predictive power.
Grmec et al.[15] 2007 Slovenia Pre-hospital	389 Consecutive adult cardiac arrests over 4 year period. $ETCO_2$ value recorded every minute beginning with post intubation (initial). 50% of patients had ROSC, 21% survived to hospital discharge. The aim of the study was to investigate various factors on outcome, including $ETCO_2$ measurements.	Prospective observational study.	ROSC (defined as ROSC and hospital admission). Survival to hospital discharge.	Both initial and final $ETCO_2$ values were significantly higher in both patients who had ROSC and patients survived to hospital discharge. In multivariate analysis: Initial $ETCO_2$ was associated with improved ROSC (OR: 22.04, 95% CI: 11.41– 42.55). Both initial (1.61, 95% CI: 1.28–2.64) and final (OR: 2.37, 95% CI: 1.67–3.37) $ETCO_2$ were associated with improved survival. All patients with ROSC had an initial $ETCO_2$ value > 1.33 kPa.

Table 1 (*Continued*)

Author, date, country, setting	Patients group	Study type	Outcomes	Key results
Lah et al.[16] 2011 Slovenia Pre-hospital	114 adult non-traumatic cardiac arrests over 3 year period (51 asphyxial, 63 primary cardiac). 72 patients had ROSC. Initial $ETCO_2$ was recorded 1 min after intubation, final $ETCO_2$ was recorded either before terminating CPR or at admission. The main aim of the study was to evaluate the difference of $ETCO_2$ pattern between asphyxial cardiac arrest and VT/VF cardiac arrest.	Prospective observational study.	ROSC (defined as ROSC and hospital admission).	Initial $ETCO_2$ was significantly higher in the asphyxia group compared to the cardiac group. In the asphyxia group, initial $ETCO_2$ was not significantly different between patients who achieved ROSC and patients who did not. In the cardiac group, initial $ETCO_2$ was significantly higher in patients who had ROSC. 5 min post CPR onwards, $ETCO_2$ was significantly higher in patients who had ROSC. This applied to both asphyxial and cardiac patients. All patients with ROSC had an initial $ETCO_2$ value > 1.33 kPa.
Mally et al.[17] Slovenia 2007 Pre-hospital	598 adult cardiac arrest victims over 6 year period. Initial $ETCO_2$ was recorded after intubation, final $ETCO_2$ was recorded at admission to hospital. 298 patients had ROSC. 126 survived to hospital discharge. The main aim of the study was to investigate the difference between vasopressin administered during CPR (n = 146) and adrenaline (n = 452) on $ETCO_2$ and MAP.	Prospective observational study.	ROSC (defined as ROSC and hospital admission). Survival to hospital discharge.	Initial, average and final $ETCO_2$ were all significantly higher in patients who had ROSC. Vasopressin resulted in significantly higher $ETCO_2$ during CPR and post ROSC. It also resulted in significantly higher MAP after ROSC. All patients with ROSC had an initial $ETCO_2$ value > 1.33 kPa. In multivariate logistic regression analysis: Initial $ETCO_2$ was associated with improved ROSC (OR: 20.35, 95% CI: 5.54 – 35.63) and hospital discharge (OR: 1.61, 95% CI: 1.28–2.64).
Grmec et al.[18] Slovenia 2003 Pre-hospital	185 adult non traumatic cardiac arrest patients (44 asphyxial, 141 primary cardiac) over 54 month period. The main aim of the study was to compare $ETCO_2$ between asphyxial cardiac arrest (PEA and asystole) and primary cardiac arrest (VF/VT).	Prospective observational study.	ROSC (defined as ROSC with hospitalisation).	For asphyxial cardiac arrest group, there was no significant difference in initial $ETCO_2$ between patients who had ROSC and patients who did not, but there was significant difference in the $ETCO_2$ at 1 min after CPR. For the primary cardiac arrest group, both initial $ETCO_2$ and $ETCO_2$ at 1 min were significantly higher in patients who had ROSC. All patients with ROSC had an initial $ETCO_2$ value > 1.33 kPa.
Ahrens et al.[19] USA 2001 In-hospital and pre-hospital	127 adult cardiac arrest patients from 6 hospitals and an air evacuation service over one year period. 55 patients had ROSC, 16 patients survived to hospital discharge.	Prospective observational study.	ROSC (defined as palpable pulse for 10 min). Survival to hospital discharge.	Initial $ETCO_2$ values were significantly higher for patients with ROSC Of 47 Patients with initial $ETCO_2$ < 1.33 kPa, 8 had ROSC and 1 survived to hospital discharge. For patients with initial $ETCO_2$ > 2.66, 87% had ROSC, approx 1/3 survived to hospital discharge. 30 patients had $ETCO_2$ < 1.33 kPa at 15 min, 1 had ROSC and survived to discharge.
Salen et al.[20] 2001 USA Emergency department	102 Non-consecutive cardiac arrest patients who underwent either cardiac sonography alone or in conjunction with capnography (53 patients) at two community hospitals EDs over 1 year period. Capnography levels were noted simultaneous to cardiac sonography. The main aim of the study was to measure the ability of cardiac sonography and capnography to predict survival of cardiac arrest.	Prospective observational study.	Survival to hospital admission.	Patients who survived to hospital admission had significantly higher $ETCO_2$. Multivariate logistic regression analysis showed that $ETCO_2$ was significant predictor of survival. For each increase of 1 torr in $ETCO_2$, the odds of surviving increased by 16% (OR: 1.16; 95% CI = 1.05 to 1.29). None of the patients with $ETCO_2$ < 16 torr (approx 2.13 kPa) survived (34 patients).

Table 1 (*Continued*)

Author, date, country, setting	Patients group	Study type	Outcomes	Key results
Mauer et al.[21] 1998 Germany Pre-hospital	RCT investigating the difference between $ETCO_2$ during standard and active compression-decompression CPR. 120 cardiac arrest patients over 30 month period. 60 patients had ROSC, 33 were admitted to hospital, and 13 survived to discharge.	Prospective randomised controlled study.	ROSC. Admission to hospital with at least 6 hour survival. Hospital discharge.	There were no differences between the study groups in the rates of ROSC, admission to hospital with 6 hour survival, and hospital discharge. In the standard CPR group, $ETCO_2$ values at 0, 2, 4, 6 and 10 min were significantly higher for patients who were admitted to hospital compared to patients declared dead on scene. In the active compression–decompression group, $ETCO_2$ values at 0, 2 and 6 min were significantly higher for patients who were admitted to hospital compared to patients declared dead on scene. All patients who survived to hospital admission had $ETCO_2 > = 2$ kPa. All patients who died on scene had $ETCO_2 < = 2.07$ kPa.
Asplin et al.[22] 1995 USA Emergency medical services	27 adult cardiac arrest patients over 13 month period. 14 patients had ROSC.	Prospective observational study	ROSC	$ETCO_2$ at 1 min and 2 min were both significantly higher in patients who had ROSC.
Entholzner et al.[23] 1996 Germany Emergency medical services	23 patients with cardiac arrest over 8 month period. 7 patients had ROSC.	Prospective observational study	ROSC	No significant difference in $ETCO_2$ values between patients with and without ROSC.
Garnett et al.[24] 1987 USA Emergency department	23 adult out-of-hospital cardiac arrest patients over 11 month period.	Prospective observational study	ROSC	No significant difference in $ETCO_2$ values between patients with and without ROSC.
Steedman et al.[25] 1990 UK Emergency department	12 adult out-of-hospital cardiac arrest patients. 5 patients had ROSC.	prospective observational study	ROSC	$ETCO_2$ values were significantly higher in patients who had ROSC.
Aichinger et al.[26] 2012 Austria Pre-hospital	42 non-consecutive adult cardiac arrest patients. The main aim of the study was to evaluate pre-hospital echocardiography in predicting outcome. Initial $ETCO_2$ values were recorded as part of the study.	Prospective observational study	ROSC	No significant difference in initial $ETCO_2$ values between patients with and without ROSC.
Krep et al.[27] 2007 Germany Pre-hospital	46 cardiac arrest patients over 8 month period resuscitated using an automated resuscitation device (AutoPulse). Only 26 patients had reliable $ETCO_2$ recordings. The main aim of the study was to evaluate the effectiveness of the AutoPulse. $ETCO_2$ measurements were used as an indicator of the device effectiveness.	Prospective observational study	ROSC	$ETCO_2$ values were significantly higher in patients who had ROSC.
Heradstveita et al.[28] 2012 Norway pre-hospital	575 cardiac arrest patients over 6 year period with capnography monitoring. 286 patients had ROSC. The main aim of the study was to explore possible factors complicating the interpretation of $ETCO_2$ during cardiac arrest.	Retrospective observational study	ROSC	$ETCO_2$ values were significantly higher in patients who had ROSC. Factors affecting $ETCO_2$ values include: Cause and initial rhythm of cardiac arrest, bystander CPR and time form cardiac arrest.
Eckstein et al.[29] 2011 USA Emergency medical services	Retrospective analysis of the records of 3121 consecutive adult non-traumatic cardiac arrests over 2 years period.	Retrospective observational study	ROSC	Initial $ETCO_2 > 1.33$ kPa and EtCO2 drop less than 25% were significantly associated with ROSC in multivariate logistic regression analysis. OR = 4.79; 95% CI = 3.10–4.42 for initial $EtCO_2 > 1.33$ kPa. OR = 2.82; 95% CI = 2.01–3.97 for $EtCO_2$ falling < 25% of baseline.

proportion of these studies; this was mainly due to the low survival rate of the studied cohort (cardiac arrest patients) resulting in small percentage of subjects achieving such outcomes, and therefore significantly smaller group to perform meaningful analysis with reliable results.

Certain similarities in strengths and weaknesses were present across the studies. Lack of blinding was a shared limitation; treating physicians were not blinded to the $ETCO_2$ values, and individuals recording the $ETCO_2$ values were not blinded to short term outcome. Therefore, observer bias may have affected the validity of the results. There was also general lack of reporting of the precision of estimates across the studies in terms of confidence intervals, limiting the ability to establish the exact clinical importance of a given results. Although not reported, confidence intervals in relation to small sample size studies are likely to be wide, limiting the conclusion of meaningful significance of such results. On the other hand, some factors enhanced the general internal validity of these studies; the fact that the outcomes measured were objective (ROSC, survival) eliminated further observer bias. In general, these studies achieved a high report rate of their outcomes of interest (commonly short term outcomes such as ROSC or ROSC associated with hospital admission), we relate this to the limited follow up period required which resulted in no or minimal loss to follow up.

A large proportion of the studies (7 out of 23) were conducted by the same group in a pre-hospital system in Slovenia.[7–9,15–18] These studies included relatively large samples ranging from 114 to 737 patients. The results of these studies were all consistent, demonstrating low $ETCO_2$ as an accurate predictor of mortality. However, these studies had similar limitations and their results should be interpreted with caution: in all but two studies, [15,16] it was not clear how the final sample was assembled from the screened patients and there was no reporting of the number of excluded patients which could have introduced selection bias. In addition, as discussed before, there was no blinding to $ETCO_2$ values and outcomes. Furthermore, none of the studies justified the sample size required to be achieved. Finally, when estimates on the $ETCO_2$ performance characteristics were reported, no measure of the precision of such estimates was included.

Different combinations of $ETCO_2$ measurement timings were examined across the studies, examples include initial, average, final and at 20 min $ETCO_2$ values. Average $ETCO_2$ is unlikely to be of any clinical use because it is technically very challenging to produce the average $ETCO_2$ value throughout the resuscitation attempt. 20 min $ETCO_2$ may have a better clinical role (assuming it is predictive of outcome) because it may allow earlier termination of resuscitation when indicating poor outcome. The initial $ETCO_2$ is potentially the most useful in clinical practice as it has the potential of aiding the prognostication process during the early stages of resuscitation. Indeed the initial $ETCO_2$ after intubation appears to be the most examined across our cohort of studies with the majority of them including initial $ETCO_2$ analysis in their results.[7–13,15–19,21,23,27–30] Some studies defined initial $ETCO_2$ as the value obtained 1 min after intubation whereas it was defined in other studies as the first value obtained after intubation. The definition of final $ETCO_2$ varied among the studies as well. Although some studies considered the final $ETCO_2$ value to be the one obtained just prior to ROSC (which makes sense from prognostication perspective), other studies [7,8,15,17] incorporated final $ETCO_2$ readings that were obtained after ROSC had occurred which is of a concern. This must have systemically affected the results comparing average and final $ETCO_2$ between the group of patients who had ROSC and the group who did not (higher for ROSC patients) and falsely augmenting the relationship between average/final $ETCO_2$ and ROSC. The variability in the studied $ETCO_2$ measurement timings along with the inconsistency of the exact definition of such measurements (such as initial and final $ETCO_2$), in addition to the varying degree of differences between the studied population (pre-hospital cardiac arrests, emergency department and in-hospital cardiac arrests), resulted in high degree of heterogeneity between the studies to reliably group data of estimates for sensitivity and specificity.

4. The association between $ETCO_2$ and outcome

There is a growing body of evidence to suggest a relationship between $ETCO_2$ values and the outcome of cardiopulmonary resuscitation. Several studies have shown that CPR $ETCO_2$ measurements were significantly higher in patients who later developed ROSC compared to patients who did not [7,15–22,25,27–29] and for patients who survived to hospital discharge compared to patients who did not.[7,9,12,15,17] Only 3 studies [23,24,26] did not confirm this relationship. These negative studies had small samples size (23, 23 and 42 patients) raising the possibility of type II error.

5. The ability of $ETCO_2$ to predict the outcome of resuscitation

The utility of $ETCO_2$ cut-off values during CPR to accurately predict the outcome of resuscitation efforts remains an area of controversy in the literature. 8 studies in total reported the performance characteristic of intra-arrest $ETCO_2$ in predicting outcomes.[7–14] For predicting ROSC, initial $ETCO_2$ cut-off value of 1.33 kPa has been shown to have a sensitivity of 100% in three large pre-hospital studies.[7–9] Although not directly reported, 100% sensitivity was also derived from the results of further 5 studies including relatively large number of patients.[15–18,21] Therefore, initial $ETCO_2$ value of less than 1.33 kPa appears to be a strong predictor of mortality. However, extreme caution has to be experienced in interpreting these results; none of the above studies reported the 95% confidence interval of the estimated 100% sensitivity to establish its precision. Furthermore, all these studies were done in pre-hospital settings, limiting the generalisability of such results to cover intra-hospital cardiac arrests or cardiac arrests arriving into the ED. All these studies apart from one were conducted by the same group in a pre-hospital system in Slovenia and had certain similar limitations in their design as discussed previously. Furthermore, one study [14] reported sensitivity of initial $ETCO_2 > 1.33$ for predicting ROSC to be only 40% (again no confidence intervals reported), although it was not primarily intended to investigate the prognostic value of $ETCO_2$. Further 2 studies [13,19] suggested that the sensitivity was 71% and <90% respectively (the value of the latter was not directly reported but derived form the reported results). Two EMS studies with moderate size samples examined the 20 min $ETCO_2$ cut-off of 1.33 kPa, they reported 100% sensitivity for predicting ROSC. [10–11] The generalisability of these two studies results to cover all cause cardiac arrest is very limited because only PEA patients were included. Emergency department studies investigating $ETCO_2$ as a mortality predictor are limited in number, they are all relatively small and lead to conflicting results; In one study,[13] a cut-off value of 2 kPa had relatively poor sensitivity of 71%, the same group later reported poor sensitivity of 41% for $ETCO_2$ cut-off value of 1.33 kPa,[14] on the other hand, a later study[20] revealed a sensitivity of 100% (not directly reported but derived from the reported study results). In summary, for $ETCO_2$ cut-off value to become an accurate predictor of death, it should sustain a very high sensitivity approaching 100% (no patients with $ETCO_2 <$ cut-off value should survive). From current evidence, this accuracy is not yet established.

Although $ETCO_2$ in cardiac arrest may have a role in the prediction of death, its ability to predict favourable outcomes (ROSC/survival) is very limited. The specificity of $ETCO_2$ in predicting ROSC at the cut-off value of 1.33 kPa was reported to be

Table 2
PPV and NPV derived from the best and worst sensitivity and specificity across a range of prevalences.

	Threshold $ETCO_2 > 1.33$ kPa				
Best-case	Sensitivity	1.00	1.00	1.00	1.00
	Specificity	0.87	0.87	0.87	0.87
	Prevalence	0.15	0.30	0.45	0.60
	PPV	0.58	0.77	0.86	0.92
	NPV	1.00	1.00	1.00	1.00
Worst-case	Sensitivity	0.40	0.40	0.40	0.40
	Specificity	0.50	0.50	0.50	0.50
	Prevalence	0.15	0.30	0.45	0.60
	PPV	0.12	0.26	0.40	0.55
	NPV	0.83	0.66	0.50	0.36

between 50% and 87% for initial $ETCO_2$,[7–9,14] and 77% for average $ETCO_2$.[12] One small study reported high specificity (98%) of initial $ETCO_2$ cut-off value of 2 kPa to predict ROSC.[13] Another study reported high specificity of 97.3% for 20 min intra-arrest $ETCO_2$ value in out-of-hospital PEA cardiac arrests,[11] but this high specificity was not replicated in another study assessing delayed $ETCO_2$ value reporting specificity of final $ETCO_2$ (either before ROSC or before termination of CPR) to be 81.4%.[9] Although the precision of such estimates was rarely reported, these specificity values do not allow accurate prediction of ROSC. Several studies reported very high specificity rate for delayed (20 min) $ETCO_2$ to predict ROSC/survival.[7,8,10] These specificity values may not be valid due to the studies design that allowed recording of 20 min $ETCO_2$ after patients achieved ROSC and included them in the analysis. This must have falsely increased the predictive value of intra-arrest $ETCO_2$ to predict ROSC.

Predicting ROSC from initial $ETCO_2$ cut-off value of 1.33 kPa had relatively wide range of sensitivities (between 40% and 100%) and specificities (between 50% and 87%) across the studies. In order to translate these values into data directly relevant to clinical practice, we derived the positive predictive values and negative predictive values of the best and worst sensitivity and specificity among varying prevalences and summarised the results in Table 2 (according to the studies included in our review, the prevalence of cardiac arrest patients achieving ROSC ranged between 0.17 and 0.63). For the best-case scenario, $ETCO_2$ value of less than 1.33 kPa would be an accurate (100%) predictor of futility of further resuscitation and $ETCO_2$ value above 1.33 kPa would predict ROSC in 58% (in low prevalence population) to 92% (in high prevalence population). In the worst-case scenario however, the cut off value 1.33 kPa cannot be used as a mortality predictor because it would wrongly predict futility of further resuscitation even in the low ROSC prevalence population (NPP of 87%, wrongly predicting futility in 13% of cases with initial $ETCO_2$ below 1.33 kPa). In fact, any deviation from the 100% sensitivity would lead to the $ETCO_2$ cut-off value of 1.33 kPa potentially wrongly predicting death; For example, a 98% sensitivity combined with specificity of 50% would lead to NPV between 92% in high ROSC prevalence population and 99% in low ROSC prevalence population, wrongly predicting death in up to 8% of cases and making the model an unreliable predictor of mortality when used in isolation.

There was a trend in the literature to indicate that, for patients with asphyxial cardiac arrest (PEA and asystole), the $ETCO_2$ values obtained immediately after intubation does not correlate with the likelihood of ROSC.[10,11,16,18] The same studies suggested that values obtained 1 min of ventilation after intubation,[18] at 5 min onwards,[16] and at 20 min all do correlate with the chance of ROSC.[10,11] This phenomenon could be explained by the fact that, during the period of asphyxia, continued cardiac output prior to cardiac arrest results in accumulation of alveolar CO_2, and therefore the initial $ETCO_2$ reflect accumulated CO_2 rather than cardiac output.

6. National and international recommendations

Leading resuscitation organisations strongly recommend the use of capnography to confirm correct placement of the endtracheal tube, to monitor the quality of CPR and to provide and early indicator of ROSC.[30] Nevertheless, their recommendation on its utility for the prediction of resuscitation outcome is much less emphasised. The International Liaison Committee on Resuscitation (ILCOR) in its international consensus (2010) acknowledges the fact that low values of $ETCO_2$ are associated with low probability of survival, the committee believes however that there are insufficient data to support or refute a specific cut-off of $ETCO_2$ as a prognostic indicator of outcome during adult cardiac arrest.[30] The view of the American Heart Association in its guidelines (2010) is not dissimilar, stating that persistently low $ETCO_2$ values below 10 mm Hg (1.33 kPa) during CPR suggest that ROSC is unlikely, again they do not comment directly on the use of $ETCO_2$ values to predict ROSC or outcome.[31] The recommendations from the European Resuscitation Council and the Resuscitation Council UK do not directly cover the utility of $ETCO_2$ values to predict outcome of resuscitation in adult patients.

7. Conclusion and implication on clinical practice

There is growing evidence in the literature demonstrating a correlation between $ETCO_2$ values during CPR and the outcome of resuscitation, and therefore, $ETCO_2$ values appears to be prognostic for short term outcome. However, the ability of $ETCO_2$ cut-off values to reliably predict the outcome of resuscitation with high accuracy is not established. $ETCO_2$ values during cardiac arrest are potentially a better predictor of mortality as opposed to a predictor of survival due to the relative high sensitivity for $ETCO_2$ cut-off values to predict ROSC and short term survival. The ideal model for mortality prediction should have a very high sensitivity to predict survival in order to lead to an accurate mortality prediction, and such high sensitivity should be maintained throughout relevant clinical studies. From current available evidence, $ETCO_2$ during resuscitation does not satisfy such prediction model and should not be used in isolation to predict mortality. However, the relative high sensitivity to predict ROSC reported suggests that $ETCO_2$ values could be used, in conjunction with other prognostic factors and clinical findings, to support the decision making process to terminate CPR. Further large multi-centre prognostic studies empowered to establish the performance of $ETCO_2$ in predicting not only short term outcomes (such as ROSC and hospital admission) but also long term outcomes (such as hospital discharge and neurological outcome) of cardiac arrest victims would no doubt have significant impact on what we currently know on the subject.

Conflict of interest statement

The authors report no conflicts of interest.

Appendix 1

Search strategy terms and details:

☐	1	MEDLINE	CAPNOGRAPHY/	814
☐	2	MEDLINE	capnograph*.ti,ab	1251
☐	3	MEDLINE	capnomet*.ti,ab	437
☐	4	MEDLINE	"end tidal carbon dioxide".ti,ab	1546
☐	5	MEDLINE	"end tidal CO_2".ti,ab	1635
☐	6	MEDLINE	"expired carbon dioxide".ti,ab	159
☐	7	MEDLINE	"expired CO_2".ti,ab	298
☐	8	MEDLINE	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	4971
☐	9	MEDLINE	HEART ARREST/	20999
☐	10	MEDLINE	"cardiac arrest*".ti,ab	18264
☐	11	MEDLINE	"heart arrest*".ti,ab	579
☐	12	MEDLINE	"cardiorespiratory arrest*".ti,ab	687
☐	13	MEDLINE	"cardio respiratory arrest*".ti,ab	100
☐	14	MEDLINE	CARDIOPULMONARY RESUSCITATION/	9859
☐	15	MEDLINE	"cardiopulmonary resuscitation*".ti,ab	8037
☐	16	MEDLINE	"cardio pulmonary resuscitation*".ti,ab	187
☐	17	MEDLINE	9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16	36789
☐	18	MEDLINE	8 AND 17	307
☐	19	MEDLINE	18 [Limit to: English Language and Humans]	207
☐	20	EMBASE	CAPNOGRAPHY/	2585
☐	21	EMBASE	capnograph*.ti,ab	1645
☐	22	EMBASE	capnomet*.ti,ab	562
☐	23	EMBASE	"end tidal carbon dioxide".ti,ab	1778
☐	24	EMBASE	"end tidal CO_2".ti,ab	2461
☐	25	EMBASE	"expired carbon dioxide".ti,ab	159
☐	26	EMBASE	"expired CO_2".ti,ab	424
☐	27	EMBASE	20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26	7321
☐	28	EMBASE	*HEART ARREST/	17391
☐	29	EMBASE	"cardiac arrest*".ti,ab	23103
☐	30	EMBASE	"heart arrest*".ti,ab	563
☐	31	EMBASE	"cardiorespiratory arrest*".ti,ab	844
☐	32	EMBASE	"cardio respiratory arrest*".ti,ab	164
☐	33	EMBASE	*CARDIOPULMONARY RESUSCITATION/	25696
☐	34	EMBASE	"cardiopulmonary resuscitation*".ti,ab	9814
☐	35	EMBASE	"cardio pulmonary resuscitation*".ti,ab	294
☐	36	EMBASE	28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35	52608
☐	37	EMBASE	27 AND 36	503
☐	38	EMBASE	37 [Limit to: Human and English Language]	307
☐	39	EMBASE	38 [Limit to: Human and English Language and (Publication Types Article or Review)]	217
☐	40	MEDLINE,EMBASE	Duplicate filtered: [18 [Limit to: English Language and Humans]], [38 [Limit to: Human and English Language and (Publication Types Article or Review)]]	424 289 Unique results 135 Duplicate results

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