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Clinical paper

Standardisation facilitates reliable interpretation of $ETCO_2$ during manual cardiopulmonary resuscitation

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Abstract

Background: Interpretation of end-tidal CO_2 ($ETCO_2$) during manual cardiopulmonary resuscitation (CPR) is affected by variations in ventilation and chest compressions. This study investigates the impact of standardising $ETCO_2$ to constant ventilation rate (VR) and compression depth (CD) on absolute values and trends.

Methods: Retrospective study of out-of-hospital cardiac arrest cases with manual CPR, including defibrillator and clinical data. $ETCO_2$, VR and CD values were averaged by minute. $ETCO_2$ was standardised to 10 vpm and 50 mm. We compared standardised (ET_s) and measured (ET_m) values and trends during resuscitation.

Results: Of 1,036 cases, 287 met the inclusion criteria. VR was mostly lower than recommended, 8.8 vpm, and highly variable within and among patients. CD was mostly within guidelines, 49.8 mm, and less varied. ET_s was lower than ET_m by 7.3 mmHg. ET_s emphasized differences by sex (22.4 females vs. 25.6 mmHg males), initial rhythm (29.1 shockable vs. 22.7 mmHg not), intubation type (25.6 supraglottic vs. 22.4 mmHg endotracheal) and return of spontaneous circulation (ROSC) achieved (34.5 mmHg) vs. not (20.1 mmHg). Trends were different between non-ROSC and ROSC patients before ROSC (–0.3 vs. + 0.2 mmHg/min), and between sustained and rearrest after ROSC (–0.7 vs. –2.1 mmHg/min). Peak ET_s was higher for sustained than for rearrest (53.0 vs. 42.5 mmHg).

Conclusion: Standardising $ETCO_2$ eliminates effects of VR and CD variations during manual CPR and facilitates comparison of values and trends among and within patients. Its clinical application for guidance of resuscitation warrants further investigation.

Keywords: CPR, $ETCO_2$, Ventilation rate, Compression depth, Capnography, ROSC, Prognosis

Introduction

End-tidal CO_2 ($ETCO_2$) has been proposed as a non-invasive indicator of the effectiveness of cardiopulmonary resuscitation (CPR) since the 2015 resuscitation guidelines[1,2]. A sudden rise of $ETCO_2$ may indicate return of spontaneous circulation (ROSC).[3–5] High and increasing $ETCO_2$ values could be associated with greater chances of ROSC and survival,[6] whereas persistently low values might indicate futility of resuscitation.[7] However, using specific cut-off values to guide resuscitation decisions is not recommended.[1,2] Instead, $ETCO_2$ changes and trends could be more useful although evidence is still limited.[6–8] All in all, $ETCO_2$ should be considered not in isolation but rather as a component of a multimodal approach.[9,10]

Clinical evidence of the usefulness of $ETCO_2$ monitoring during resuscitation is limited. Several factors affect the interpretation of measured $ETCO_2$ values and trends within and among patients, including the effect of chest compressions (CCs) and ventilations.[5,8] CCs and ventilations affect the generation and extraction of CO_2 from the patient in cardiac arrest, respectively. Observational studies have shown the predominant linear contribution of chest compression depth (CD) to $ETCO_2$.[11–13] Conversely, increasing ventilation rates (VR) contributes to exponential decrease of measured $ETCO_2$ and is a major confounder of $ETCO_2$.[11,12,14–16] Therefore, variations

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of CD and VR in manual CPR (in which ventilations and CCs are provided manually, as opposed to mechanical CPR) limit the clinical interpretation of $ETCO_2$ during resuscitation. Recently, mathematical models that account for changes in CD and VR have been proposed and validated retrospectively with human out-of-hospital cardiac arrest (OHCA) data,[13,17,18] but their value during resuscitation remained to be examined.

In this context, the aim of this observational study was to standardise $ETCO_2$ to fixed VR and CD, removing the masking effects consequence of their variations during manual CPR, and to explore its clinical utility compared to measured $ETCO_2$. We assessed their differences for various populations, and analysed trends of ROSC and non-ROSC patients during resuscitation. Standardised $ETCO_2$ could provide a more reliable observation of the physiological response of each patient and facilitate comparisons among different patients. Ultimately, our findings could help to improve the clinical usefulness of $ETCO_2$ values and trends during manual CPR.

Materials and methods

Data collection and inclusion

Data were obtained from a large database of adult (≥18 years old) OHCA resuscitation episodes, treated by Tualatin Valley Fire & Rescue (Tigard, OR, USA), a first response advanced life support emergency medical services (EMS) agency in Oregon, USA, from 2006 through 2017. The database is part of the Resuscitation Outcomes Consortium Epidemiological Cardiac Arrest Registry collected by the Portland Regional Clinical Center with the approval of the Oregon Health & Science University Institutional Review Board (IRB00001736). Anonymised clinical data (demographics, interventions and outcomes) were linked to the recordings.

All episodes were collected with Heartstart MRx monitor-defibrillators incorporating QCPR technology (Philips Healthcare, USA) for real-time feedback on CC depth, rate and recoil, and side-stream capnography (Microstream, Oridion Systems Ltd., Israel). Continuous CCs with interposed ventilations were provided manually by TVF&R field providers after an advanced airway had been secured, with either a supraglottic device (SGA) or an endotracheal tube (ETT). Only episodes with concurrent CO_2, electrocardiogram (ECG), CD, and transthoracic impedance (TI) signals were included in the study.

Segment selection and annotation

Signals were visually inspected to include episodes with reliable capnogram in which ventilation and $ETCO_2$ values could be annotated. From the valid episodes, individual CCs and ventilations were detected automatically in the CD and the capnography signals, respectively. Chest compression series were delimited and the maximum depth of each compression was annotated, as well as $ETCO_2$ values at every ventilation instance. Subsequently, the capnogram of each episode was divided into segments of 1-min in length and segments characterised by their mean $ETCO_2$, CD and VR values.

Episodes with less than 1,000 CCs or 6 consecutive 1-min segments were discarded, in order to have sufficiently long series of values for assessing the evolution of parameters over the course of resuscitation. ECG and TI signals were used to visually identify ROSC (a regular ECG rhythm combined with absence of CCs) and non-ROSC periods within the episodes, further validated with EMS reports of the patients.

Standardisation of $ETCO_2$

Each minute $ETCO_2$ value was standardised to reference VR and CD values, according to the models described previously,[13,18] using a decay coefficient $k = 0.9$[17], a VR of 10 vpm and a CD of 50 mm. The resulting standardised minute $ETCO_2$ value, ET_s, constituted the novel metric under study. The original measured value was termed ET_m for comparison.

Fig. 1 shows two examples of the standardisation process: one for a non-ROSC patient who died in field and another for a patient who reached ROSC after 12 min of resuscitation but died in the emergency department (ED). Differences between ET_m and ET_s values and trends are noticeable in either case.

Data analysis

ET_m and ET_s were analysed for all patients, disaggregated by sex, age group, initial shockable vs. non-shockable rhythm, advanced airway type and whether ROSC was achieved in the field (i.e. prior to departure from the cardiac arrest scene). Inter-patient characteristics were studied via distributions of ET_m, ET_s, VR and CD, described by their median and 25th–75th percentiles (IQR). Intra-patient variability was determined with the coefficient of variation (CV). Absolute and relative differences were calculated and assessed using Kruskal-Wallis tests, treating p-values lower than 0.05 as significant.

The evolution of ET_s was assessed for patients categorised into non-ROSC, sustained ROSC (these did not lose pulse at least until arrival to the ED, and received no CCs at least from two minutes after ROSC was annotated onwards) and ROSC with rearrest. Specifically, we analysed the following 4 non-overlapping zones throughout resuscitation:

- Zone I: interval of up to 15 min before zone II, at the beginning of the recording, without spontaneous circulation.
- Zone II: interval of 3 min preceding the peak of ET_s around ROSC during spontaneous circulation.
- Zone III: interval of 3 min following the peak of ET_s during spontaneous circulation.
- Zone IV: interval of 3 min before CCs were resumed for rearrest patients; and 10 min after the ET_s peak for sustained patients. The latter time that corresponds to the percentile 75th when rearrest patients had CCs resumed.

For every episode, we computed the average ET_s in zones I and IV and the peak value in zones II and III, in mmHg. We also calculated the absolute variation of ET_s from the beginning to the end of each zone in mmHg/min and its relative variation after normalisation by the initial ET_s of the zone in %/min.

Results

Data characteristics

From the initial 1,036 episodes, only 403 had concurrent capnogram, CD, TI and ECG signals, at least 1,000 CCs and a reliable capnogram. Requiring 6 min of consecutive 1-min segments further reduced the sample size to 287. The total duration of the signals analysed was 7,203 min, with 40,220 ventilations and 388,224 CCs. The mean (standard deviation) duration of the episodes was 25.1 (9.8) min.

Characteristics of the patients are reported in Table 1. Median age was 66 (55–76) years old and 30% were female. ETT was used

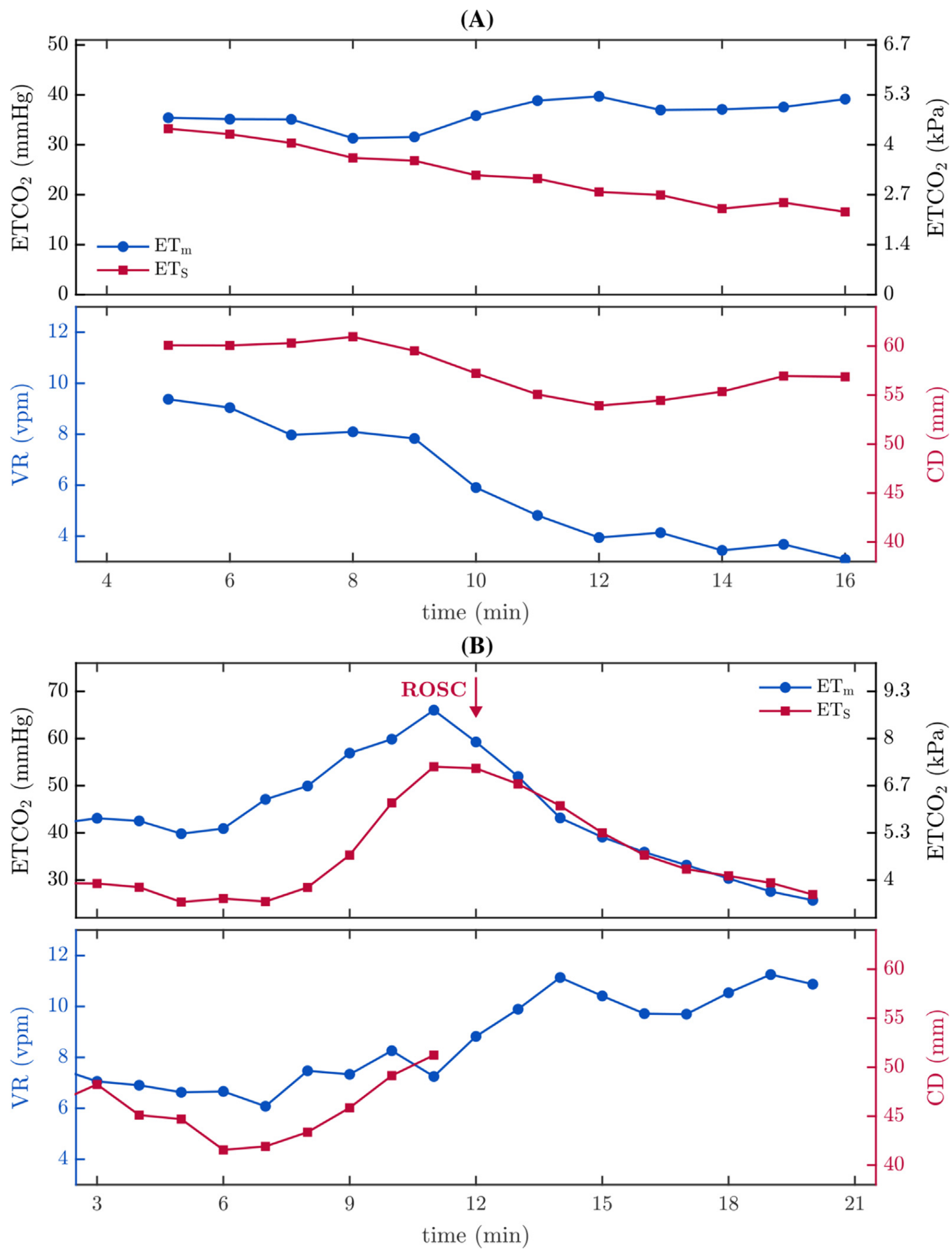

Fig. 1 – Comparison of standardised and measured $ETCO_2$ for single patients. The top panels depict ET_m (in blue) and ET_s (in red) during the resuscitation attempt. The bottom panels show the corresponding minute average VR and CD values. In (A) we show the case of a 72yo female with initial rhythm being PEA, intubated with ETT, who never reached ROSC and died in field. ET_m is rather constant, slightly upwards, but the standardised trend is clearly downwards, as ET_s reflects. Then, in (B) we show the case of a 86yo female with initial shockable rhythm, intubated with SGA, who had ROSC 12 min into resuscitation and expired in ED. ET_m was larger than ET_s for most of the episode and the trend of ET_m towards ROSC initiates earlier than that of ET_s. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

in 48% of the patients, while SGA was employed in 44%. Initial EMS rhythm was asystole in 46% of the episodes, pulseless electrical activity in 26% and shockable in 28%. ROSC was achieved at any time in the field in 28% of the patients, and was sustained in 54% of these cases. Death occurred in the field in 34% of the episodes, in the emergency department in 44% and after hospital admission

Table 1 – Patient characteristics for the included episodes (n = 287). ROSC refers to any ROSC event in the field. Definition of sustained and rearrest ROSC for the study are described in section 2.4.

Characteristic	Observed Value
Age (y), median (IQR)	66 (55–76)
Sex, n (%)	
Female	86 (30)
Male	201 (70)
Advanced airway type, n (%)	
Endotracheal tube (ETT)	136 (48)
Supraglottic King LT-D (SGA)	127 (44)
Unknown	24 (8)
Initial rhythm, n (%)	
Shockable (VF/VT)	80 (28)
Pulseless electrical activity	76 (26)
Asystole	131 (46)
Return of Spontaneous Circulation (ROSC), n (%)	
Any ROSC	80 (28)
Sustained	43 (15)
Rearrest	38 (13)
Disposition, n (%)	
Died in field	97 (34)
Died in emergency department	127 (44)
Died after hospital admission	53 (19)
Discharged alive	10 (3)

in 19%. Only 3% of the patients survived to hospital discharge. Note this low survival rate reflects outcomes in this subset of cases where patients received at least 1,000 CCs.

Measured vs. standardised ETCO$_2$ values

Fig. 2 shows the distributions (median and IQR) of ET_m and ET_s values for the total population, as well as stratified by sex, age group, initial shockable or non-shockable rhythm, airway type and any ROSC achieved in the field. Corresponding distributions of VR and CD are depicted for better understanding of the basis of standardisation.

Overall, median (IQR) ET_s was 24.2 (16.2–35.0) mmHg while ET_m was 31.3 (21.2–42.0) mmHg, i.e. ET_s was 7.2 mmHg, or 24%, below ET_m. VR was 8.8 (7.4–10.8) vpm, smaller in median than the 10 vpm reference and with a relatively large IQR, indicating inter-patient dispersion. Its median CV was 0.30, reflecting large variability within each patient. CD was 49.8 (43.0–55.5) mm, close to the 50 mm reference, with lower IQR and CV values (0.10) than VR. Therefore, in our database, the main decrease in ETCO$_2$ from standardisation was attributable to VR.

ET_s was lower than ET_m for all subgroups. Standardisation enlarged ET_s separation between males and females (25.6 vs. 22.4 mmHg, p = 0.26) compared to ET_m (31.3 vs. 31.3 mmHg). VR was slower for females than for males (8.3 vs 8.9 vpm, p = 0.03) and with less dispersion (IQR), even though variability was slightly greater (CV of 0.32 vs 0.29, p = 0.03). We found no differences in CD relative to sex; thus, VR affected standardisation more in females than in males.

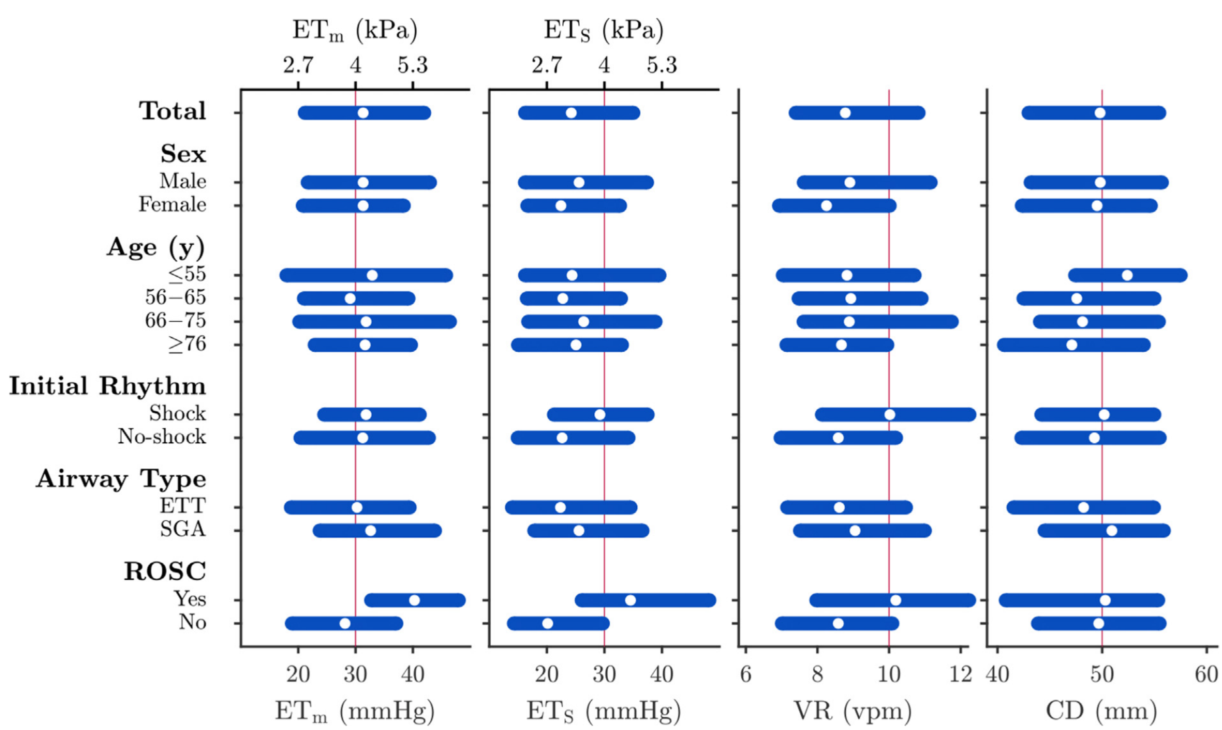

Fig. 2 – Distributions (median and IQR) of the measured (ET_m) and standardised ET_s values, and the corresponding VR and CD, for the patient cohort, and disaggregated by sex, age group, initial shockable vs. non-shockable rhythm, airway type SGA vs ETT, and if any ROSC was achieved in the field. The vertical red lines indicate visual references of ETCO$_2$ at 30 mmHg, and the 10 vpm and 50 mm values used for standardisation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

CD decreased as age increased ($p \ll 0.05$), but we observed no differences in VR ($p = 0.38$) or ET_s ($p = 0.70$).

ET_s was significantly higher in patients with initial shockable rhythm than in those with non-shockable rhythm (29.1 vs. 22.7 mmHg, $p = 0.01$) No differences were observed before standardisation. Patients with initial non-shockable rhythms were ventilated at lower VR (8.6 vs. 10 vpm, $p \ll 0.05$). VR variability was higher in patients presenting initial non-shockable rhythm (CV of 0.31 vs. 0.27, $p = 0.01$). No differences in CD were observed in relation to initial rhythm ($p = 0.64$).

ET_s was also significantly larger in ROSC than in non-ROSC patients (34.5 vs. 20.1 mmHg, $p \ll 0.05$). Median VR for ROSC patients was close to the reference, while non-ROSC patients were ventilated at lower VR (10 vs. 8.6 vpm, $p \ll 0.05$). There were no differences in CD in relation to ROSC ($p = 0.51$).

Finally, ET_s was higher for SGA than ETT intubation (25.6 vs. 22.4 mmHg, $p = 0.03$). VR was similar (9.1 vs 8.6 vpm, $p = 0.13$) and differences in CD small (50.9 vs. 48.2, $p = 0.04$).

Evolution of ET_s during resuscitation

The top panels of Fig. 3 show the trends of ET_s over the course of resuscitation, for the non-ROSC, the sustained ROSC and the patients with rearrest. Since ROSC timelines were aligned at ROSC time (t_{ROSC}), the instants before and after the onset are noted with negative and positive minute values, respectively. The middle panels show trends of VR and CD for the three groups. The main lines represent the median values and the shadowed strips delimit the IQR intervals. The bottom panels depict the temporal dynamics of patients entering and exiting the analysis, from the beginning of reliable capnographic data to the end of the recording.

A general slightly decreasing trend of ET_s was observed for the non-ROSC patients, while a clear rise starting some minutes before t_{ROSC} was evident for both types of ROSC patients. In the non-ROSC group VR decreased over the first 10 min of resuscitation until reaching a consistent value of around 8 vpm. In contrast, in the ROSC group VR increased from below 8 vpm to around 12 vpm at the moment of ROSC. CD was consistently close to 50 mm in non-ROSC and sustained ROSC patients but a transient decrease in median CD was observed in patients who rearrested.

The evolution of ETs for the 4 zones of section 2.4 is summarised in Table 2. In zone I, ROSC patients presented statistically significantly higher ET_s values than non-ROSC patients (27.7 vs 20.5 mmHg, $p = 0.01$), while no significant differences existed between patients with sustained ROSC and those presenting rearrest. Absolute and relative variations of ET_s were also significantly different between non-ROSC and ROSC groups (–0.3 vs + 0.2 mm Hg/min, $p \ll 0.05$; –1.4 vs + 0.7%/min, $p \ll 0.05$), but not between patients with sustained ROSC and those with rearrest. Then, the peak ET_s value of zones II-III was higher for sustained compared to rearrest patients (53.0 vs 42.5 mmHg, $p = 0.01$). In zone II, absolute and relative ET_s variations did not distinguish sustained ROSC from rearrest patients. In zone III absolute (–1.5 vs –2.5 mmHg/min, $p = 0.03$) and relative variations (–2.8 vs –6.5, $p \ll 0.05$) were significantly different between sustained ROSC and rearrest patients. To end, in zone IV, ET_s was significantly higher for sustained patients (43.9 vs 29.0, $p = 0.01$), absolute variations were different between sustained and rearrest groups (–0.7 vs –2.1 mmHg/min, $p = 0.03$) and relative variations were even more significantly different (–1.9 vs –9.4%/min, $p = 0.01$).

Discussion

CPR aims to maximise the chances of survival and positive neurological outcomes for patients experiencing cardiac arrest. Monitoring physiological variables during resuscitation and adapting interventions accordingly may be beneficial. Capnography, a non-invasive method of measuring $ETCO_2$, reflects cardiac output and organ perfusion. However, the usefulness of $ETCO_2$ in predicting outcomes and guiding resuscitation efforts is limited. According to current guidelines, neither $ETCO_2$ cut-off values nor trends should be used in isolation as mortality predictors, to decide to cease resuscitation, or to anticipate ROSC. A large number of factors affect $ETCO_2$ values and trends, among which those associated to ventilations and CCs are well known. Ventilation affects $ETCO_2$ as a consequence of alterations in tidal volume (TV) and VR.[14] These effects have been modelled at least in two relevant studies: on the one hand, Gazmuri et al. analysed how VR and TV (i.e. minute-volume) jointly affect $ETCO_2$ in a swine model[14]; on the other hand, Ruiz de Gauna et al. proposed a mathematical relation between $ETCO_2$ and VR, and validated it retrospectively on 508 adult OHCA episodes.[18] Differences between both models were found to be small. Regarding the influence of CCs on $ETCO_2$, several works have emphasised the predominant influence of CD in changing $ETCO_2$ compared to compression rate (CR).[11–13] The effects of CD and CR have also been modelled and validated retrospectively.[13] The prevalent absence of volume information in pre-hospital settings has motivated us to focus on the aforementioned models for VR and CD alone. Increasing VR leads to a decrease in $ETCO_2$[11,12,14–17], not necessarily related to poor prognosis. A rise of $ETCO_2$ may be due to slower VR, rather than reflecting better perfusion or anticipating ROSC. In addition, CCs contribute to $ETCO_2$ production in the absence of circulation.[11–13] Without controlling VR and CD, the interpretation of $ETCO_2$ is challenging, if not unreliable, specially to guide clinical decisions.

Our study proposes the standardisation of measured $ETCO_2$ values to constant VR and CD during manual CPR, enhancing the role of $ETCO_2$ in reflecting the status of the patient. Standardised $ETCO_2$ values were lower than measured irrespective of the group, with an overall median difference of 7.2 mmHg, or 24%. We found significant differences in ET_s when stratifying by initial rhythm, airway type and achievement of ROSC in the field. Moreover, median VR was statistically different according to sex, initial rhythm and ROSC. In contrast, we only found differences in CD related to age, a slight decrease in older patients. Additionally, the observed inter-patient dispersion and intra-patient variability of VR were remarkable (IQR of 21.7–44.1 and median CV of 0.30) compared to CD (43.0–55.5 and 0.10). Thus, VR was the greatest confounder in our database, possibly because rescuers had real-time feedback on CCs, while VR was displayed as a number on the monitor and may have gone unnoticed. Prospectively, variations in VR could be reduced by reinforcing feedback on ventilation quality, or their masking effect could be eliminated by adding information on real-time standardised $ETCO_2$ values for better assessment of the patient condition and evolution.

Removing the effects of dispersion and variability of VR and CD results into dramatic alterations of measured values and trends, of which Fig. 1 is very representative. In this figure, although ET_m for the non-ROSC patient is fairly constant, or even slightly upwards, this is likely due to the effects of the manoeuvre. By reducing VR

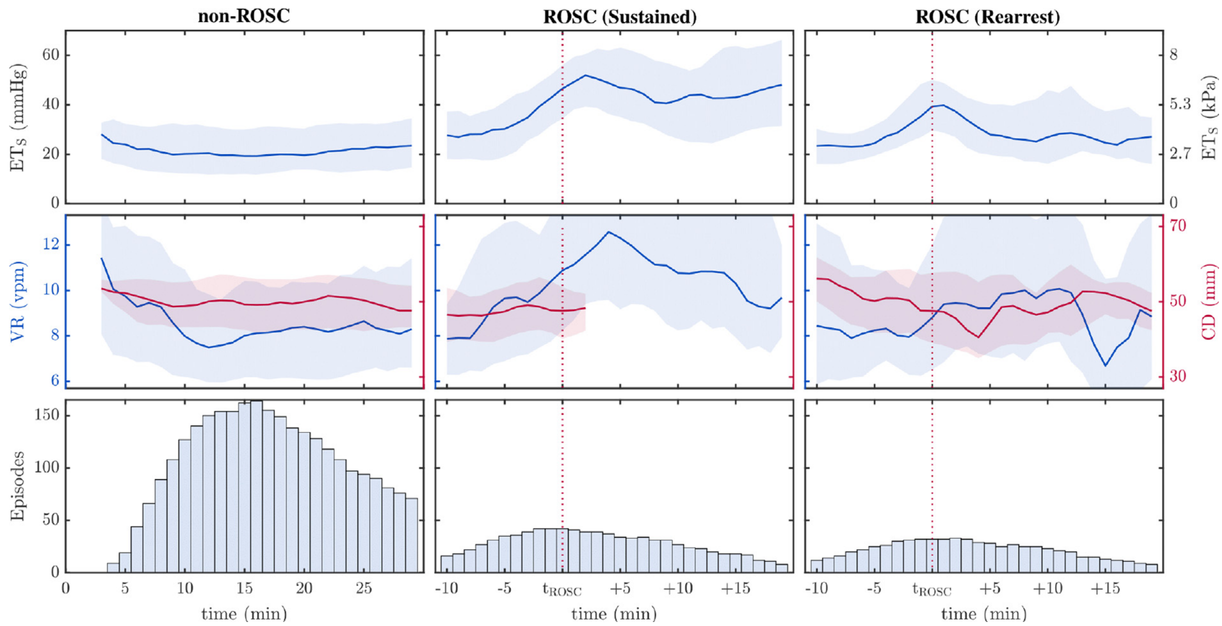

Fig. 3 – Evolution of ET_s throughout the resuscitation attempt for non-ROSC and ROSC (sustained and rearrest) patients. The line depict the median and shadowed areas the IQR. ROSC cases are aligned at ROSC time. Middle pannels show the evolution of VR and CD. Bottom pannels show the dynamics of patients entering and exiting the analysis.

Table 2 – Evolution of ET_s in different zones. Zone I: interval of up to 15 min with no ROSC aligned at the beginning of the episode; Zone II: ROSC interval of 3 min before the ET_s peak around ROSC; Zone III: ROSC interval of 3 min after ET_s peak; Zone IV: 3 min interval before chest compressions were resumed for rearrest cases and 10 min after the ET_s peak for sustained ROSC. Values are in mmHg and represent mean ET_s in zones I and IV and peak ET_s in zones II and III. Absolute variations are given in mmHg/min and relative variations in %/min.

	Values	Abs. variation	Rel. variation
Zone I			
non-ROSC	20.5 (14.1, 30.1)	–0.3 (–0.9, +0.3)	–1.4 (–3.4, +1.2)
ROSC (all)	27.7 (18.9, 34.4)	+0.2 (–0.5, +1.4)	+0.7 (–1.3, +8.3)
p-value	$\ll 0.05$	$\ll 0.05$	$\ll 0.05$
ROSC (sustained)	30.2 (19.6, 39.0)	+0.2 (–0.4, +1.8)	+0.7 (–1.2, +9.6)
ROSC (rearrest)	23.9 (18.8, 30.0)	+0.4 (–0.6, +1.1)	+0.5 (–2.8, +6.9)
p-value	0.15	0.35	0.43
Zone II			
ROSC (all)	47.1 (35.5, 58.0)	+4.1 (+2.2, +6.3)	+11.9 (+6.1, +19.5)
ROSC (sustained)	53.0 (43.4, 60.7)	+4.5 (+3.0, +6.6)	+10.7 (+6.5, +21.0)
ROSC (rearrest)	42.5 (31.5, 52.7)	+3.2 (+1.6, +5.5)	+12.1 (+5.2, +19.2)
p-value	0.01	0.14	0.70
Zone III			
ROSC (all)	47.1 (35.5, 58.0)	–1.7 (–3.4, –0.7)	–3.9 (–7.7, –1.6)
ROSC (sustained)	53.0 (43.4, 60.7)	–1.5 (–2.4, +0.6)	–2.8 (–5.1, +1.4)
ROSC (rearrest)	42.5 (31.5, 52.7)	–2.5 (–4.1, –1.3)	–6.5 (–10.6, –3.1)
p-value	0.01	0.03	$\ll 0.05$
Zone IV			
ROSC (all)	38.8 (27.9, 52.2)	–1.1 (–2.2, +0.2)	–2.8 (–8.8, +0.3)
ROSC (sustained)	43.9 (32.3, 53.5)	–0.7 (–1.2, +0.2)	–1.9 (–2.9, +0.3)
ROSC (rearrest)	29.0 (22.6, 39.3)	–2.1 (–4.8, –0.2)	–9.4 (–13.5, –0.4)
p-value	0.01	0.03	0.01

and increasing CD, the rescuer possibly tried to maintain measured $ETCO_2$ levels steady. However, the standardised trend is downwards, as ET_s clearly reflects. For the ROSC patient, ET_m was mostly larger than ET_s, and had a trend towards ROSC that initiated earlier but was less pronounced than that of ET_s. All these are again consequences of the VR up to minute 12 being well below 10 vpm and CD less than 50 mm, with large variability during the resuscitation attempt.

We observed significant differences in the mean evolution of ET_s in non-ROSC patients compared to ROSC patients. The group without ROSC displayed lower standardised values and a decay rate of – 1.1%/min for normalized ET_s compared to an increase rate of + 0.7%/min for ROSC patients in the absence of circulation (Zone I). The decay might be a reflection of the progressive deterioration of perfusion, leading to cellular ischaemia and eventual brain damage,[19,20] and could be studied as a potential indicator of futility. In contrast, the increasing ET_s rate in the ROSC group is in line with recent studies reporting that increasing values of $ETCO_2$ are predictors of ROSC,[21] survival to hospital discharge[22] and survival with good neurological outcome.[23] Furthermore, a few minutes prior to the ET_s peak around ROSC (zone II), all ROSC patients experienced a marked ET_s growth of + 12%/min, regardless of whether ROSC was sustained or not. Lastly, ET_s reduced in the first minutes after the ET_s peak around ROSC (zone III), more so in rearrest patients, for whom it ended up plummeting at a rate of –9.4%/min (zone IV), probably reflecting perfusion failure due to absence of pulse and CCs. Earlier detection of these negative evolutions could drive interventions to prevent rearrest, such as starting low doses of epinephrine or norepinephrine to boost perfusion.

ET_s should be considered as an additional indicator to ET_m on the physiological condition and evolution of the patient over the course of resuscitation. Further studies are needed in order to determine reliable reference cut-off values and trends of ET_s that could help guidance in clinical decisions. The results of those studies could eventually be incorporated in successive updates of resuscitation guidelines.

Limitations

Our standardisation model was adjusted empirically based on our previous works. Selecting other reference VR and CD would have changed ET_s results. Thus, common references are required for comparability among studies. We chose these values according to current resuscitation guidelines. Many episodes were discarded due to strict inclusion criteria, which may cause selection bias. Analysis would benefit from additional data.

The absence of tidal volume information prevented us from quantifying minute ventilation and, therefore, its impact on the standardisation model. Other potential confounding factors were not taken into account, such as the aetiology of arrest, which might affect initial $ETCO_2$ levels, or administration of drugs like epinephrine, known to cause a notable decrease in $ETCO_2$ levels.[24,25]

Conclusions

ET_s was significantly different from ET_m, overall and among populations. Standardisation of $ETCO_2$ to constant VR and CD allows for compensating inter-patient dispersion and intra-patient variability during manual CPR. Therefore, ET_s may improve the reliability of comparative studies, and could help guide clinical decision during the course of resuscitation since it better reflects the status of the patient. Its usefulness as an indicator of ROSC or termination of resuscitation would merit further investigation by conducting appropriate prospective studies.

CRediT authorship contribution statement

Jose Julio Gutiérrez: Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jose Antonio Urigüen:** Conceptualization, Methodology, Formal analysis, Investigation, Software, Validation, Writing – original draft, Writing – review & editing. **Mikel Leturiondo:** Writing – review & editing, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Camilo Leonardo Sandoval:** Writing – review & editing, Visualization, Validation, Data curation. **Koldo Redondo:** Writing – review & editing, Visualization, Validation. **James Knox Russell:** Writing – review & editing, Validation, Resources, Methodology, Formal analysis, Data curation. **Mohamud Ramzan Daya:** Writing – review & editing, Validation, Supervision, Resources, Methodology. **Sofía Ruiz de Gauna:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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