Association between Prehospital CPR Quality and End-Tidal Carbon Dioxide Levels in Out-of-Hospital Cardiac Arrest

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ABSTRACT

Introduction: International Guidelines recommend measurement of end-tidal carbon dioxide ($EtCO_2$) to enhance cardiopulmonary resuscitation (CPR) quality and optimize blood flow during CPR. Numerous factors impact $EtCO_2$ (e.g., ventilation, metabolism, cardiac output), yet few clinical studies have correlated CPR quality and $EtCO_2$ during actual out-of-hospital cardiac arrest (OHCA) resuscitations. The purpose of this study was to describe the association between $EtCO_2$ and CPR quality variables during OHCA. **Methods:** This is an observational study of prospectively collected CPR quality and capnography data from two EMS agencies participating in a statewide resuscitation quality improvement program. CPR quality and capnography data from adult ($\geq$18 years) cardiac resuscitation attempts (10/2008–06/2013) were collected and analyzed on a minute-by-minute basis using RescueNet™ Code Review. Linear mixed effect models were used to evaluate the association between (log-transformed) $EtCO_2$ level and CPR variables:

chest compression (CC) depth, CC rate, CC release velocity (CCRV), ventilation rate. **Results:** Among the 1217 adult OHCA cases of presumed cardiac etiology, 925 (76.0%) had a monitor-defibrillator file with CPR quality data, of which 296 (32.0%) cases had >1 minute of capnography data during CPR. After capnography quality review, 66 of these cases (22.3%) were excluded due to uninterpretable capnography, resulting in a final study sample of 230 subjects (mean age 68 years; 69.1% male), with a total of 1581 minutes of data. After adjustment for other CPR variables, a 10 mm increase in CC depth was associated with a 4.0% increase in $EtCO_2$ ($p < 0.0001$), a 10 compression/minute increase in CC rate with a 1.7% increase in $EtCO_2$ ($p = 0.02$), a 10 mm/second increase in CCRV with a 2.8% increase in $EtCO_2$ ($p = 0.03$), and a 10 breath/minute increase in ventilation rate with a 17.4% decrease in $EtCO_2$ ($p < 0.0001$). **Conclusion:** When controlling for known CPR quality variables, increases in CC depth, CC rate and CCRV were each associated with a statistically significant but clinically modest increase in $EtCO_2$. Given the small effect sizes, the clinical utility of using $EtCO_2$ to guide CPR performance is unclear. Further research is needed to determine the practicality and impact of using real-time $EtCO_2$ to guide CPR delivery in the prehospital environment. **Key words:** capnography; end-tidal carbon dioxide; cardiopulmonary resuscitation; cardiac output; out-of-hospital cardiac arrest

INTRODUCTION

Out-of-hospital cardiac arrest (OHCA) is a major global public health problem with approximately 6 million cases occurring globally each year.[1] Inconsistent cardiopulmonary resuscitation (CPR) quality is believed to contribute to poor and variable outcomes.[2,3] During cardiac arrest, CPR functions to deliver substrate to vital organs. Animal studies have shown that end-tidal carbon dioxide ($EtCO_2$) detected during CPR is primarily dependent on pulmonary blood flow and is, therefore, a potential surrogate marker of perfusion during CPR.[4–6] However, there are few clinical studies specifically evaluating the association between CPR quality and $EtCO_2$ during prehospital resuscitation.[7]

Current guidelines recommend measuring CPR performance metrics as well as the patient's physiological response during resuscitation. A 2013 American Heart Association (AHA) consensus statement defined adult high-quality CPR using specific target metrics: chest compression (CC) depth >50 millimeters, CC

rate >100 compressions per minute, CC fraction >80%, avoidance of leaning (full chest recoil), and avoidance of excessive ventilation (rate <12 breaths per minute, volume only enough to see chest wall rise.[2] The consensus statement recommends using $EtCO_2$ as the primary physiological metric (when neither an arterial nor a central venous catheter is in place) and "...titrating CPR performance to a goal of $EtCO_2$ >20 mmHg while not excessively ventilating the patient."[2] However, the understanding of the relationship between CPR performance variables, $EtCO_2$ and outcomes is incomplete. The purpose of this study was to describe the association between $EtCO_2$ and CPR quality variables during prehospital cardiac resuscitation.

METHODS

Study Setting

Data for this study were collected from two Emergency Medical Services (EMS) agencies in Arizona. Mesa Fire and Medical Department responds to 70,000 9-1-1 calls per year in a large suburban city (population 439,000). Each crew includes two emergency medical technician (EMT) Basics (EMT-B) and two EMT Paramedics (EMT-P). Guardian Medical Transport (GMT) responds to approximately 14,000 9-1-1 calls per year in suburban and rural areas (population 80,000). GMT dispatches a crew of at least one EMT-B and one EMT-P to emergency calls. Both EMS agencies use a minimally interrupted cardiac resuscitation (MICR) protocol as their standard approach to adult patients with OHCA of suspected cardiac etiology. The MICR protocol remained unchanged during the enrollment period and has been described in detail previously.[8,9]

Study Design and Population

This was a prospective, observational cohort study of adult (≥18 years old) OHCA patients who had prehospital CPR initiated between October 7, 2008 and June 30, 2013. After review of EMS patient care reports (PCR) and hospital records, cases were excluded from analysis if: the patient was less than 18 years old or if the cause of the arrest was determined to be non-cardiac (e.g., known respiratory arrest, suicide, trauma, drowning, drug overdose).

During the study period, both EMS agencies participated in a prehospital initiative (described in detail previously) aimed at improving CPR quality by implementing scenario-based training (SBT) and real-time audiovisual feedback.[10] The SBT emphasized a team approach to resuscitation and compliance with the parameters of high-quality CPR based on the 2010 AHA guidelines.[11]

Data Collection

Both agencies were equipped with defibrillators integrated with accelerometer-based technology (E-series; Zoll Medical Corporation) and sidestream $EtCO_2$ adaptors (LoFlo Sidestream CO_2 Module; Philips/Respironics) enabling electronic recording of minute-by-minute CPR quality variables (CC depth, CC rate, CCRV, and ventilation rate) and $EtCO_2$ data. The ventilation rate for each minute was determined from the capnogram. Following each use, EMS personnel were instructed to download the monitor file and electronically submit to the data coordinator for file review via a secure server.

The Save Hearts in Arizona Registry and Education (SHARE) Program is an Arizona Department of Health Services (ADHS)-sponsored public health initiative that was implemented in 2005 as a statewide quality improvement program.[12] Both the ADHS Human Subjects Review Board and the University of Arizona Institutional Review Board have determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitute Human Subjects Research and have approved the publication of de-identified data. The project is registered at ClinicalTrials.gov #NCT01258244.

Data Processing

Event files with minute-by-minute CPR quality data and capnography data, when present, were uploaded to the SHARE database using RescueNet[TM] Code Review (Zoll Medical Corporation). SHARE uses an Utstein-style database and links electronic event data, PCRs, and hospital outcomes.[8,12] Periods where the patient had return of spontaneous circulation (ROSC) were identified by data coordinators through review of PCR reports, CPR quality data, capnography data, and electrocardiogram review. Data during the following timeframes were excluded from analysis: the first minute after intubation ($EtCO_2$ levels in this minute also reflect accumulated CO_2), and minutes with spontaneous circulation.

Due to the technical issues inherent to capnography (such as leaks or obstructions between the breathing system and sampling system, kinks or damage to tubing, condensate forming on walls of tubing secondary to changes in temperature or patient secretions),[13] a manual minute-by-minute analysis of the capnogram was performed by two data coordinators. Capnograms were evaluated for typical waveform structure: baseline, ascending phase, alveolar plateau, and descending phase.[14] Minutes were marked as 'artifact' if they were inconsistent with physiologic waveform shape suggesting monitoring equipment malfunction.[15]

To determine reliability between the two data coordinators' individual assessments of minutes with

capnography, an inter-rater reliability (IRR) test was conducted on a random sample of 20 code monitor files (each file contained at least 4 continuous minutes of capnography data). The analysts' crude agreement in these 20 files was 95.9% (95% confidence interval-CI = 91.7%–98.3%). The calculated Kappa rating was 0.567 (95% CI = 0.281–0.781).

All minutes of capnography were reviewed and marked as "valid" or "artifact" by both coordinators. Minutes were excluded if either one or both of the coordinators rated the minute as artifact. Cases were only included for final analysis if they had at least one minute of CPR data and corresponding valid capnography.

Statistical Analysis

Demographics, event characteristics, and clinical outcomes were summarized by either count and proportion (for categorical variables) or median and range (for continuous variables), and were compared between included and excluded subjects using Fisher's exact test (for categorical data) and Wilcoxon rank-sum test (for continuous data). In addition, $EtCO_2$ levels and all CPR variables were compared between sub-categorized groups (stratified by shockable initial rhythm and prehospital ROSC) using the Wilcoxon rank-sum test.

$EtCO_2$ values were checked graphically and log transformation was applied to achieve approximate normality. Scatter plots and locally-weighted polynomial regressions were used to graphically check the relationship between transformed $EtCO_2$ and each CPR variable (CC depth, CC rate, CCRV, and ventilation rate), and time (in minutes). Linear mixed effect models were used to evaluate the association between transformed $EtCO_2$ level and each CPR variable, with a random intercept for each case and a spatial power covariance structure for measurements over time. Both unadjusted and adjusted models were fitted for each CPR variable, with the unadjusted model including the CPR variable and time only, and the adjusted model also including other CPR variables. CC depth and CCRV were highly correlated with each other; therefore, when one of them was evaluated, the other was excluded from the adjusted model. Both were included in the adjusted models when CC rate or ventilation rate were being evaluated. Time (in minutes) was included as a linear effect in each model. Then, as a sensitivity analysis, each individual minute was allowed to have a separate effect on $EtCO_2$. All statistical tests were two-tailed with α set at 0.05.

RESULTS

At total of 1504 OHCA cases were treated during the study period and 1217 were adult OHCA of presumed cardiac etiology (Figure 1). Among these, 925 (76.0%) had a monitor-defibrillator file containing CPR quality data. Of these, 296 (32.0%) had ≥ 1 minute of capnography data with corresponding CPR quality data during the CPR period. After capnography quality review, 66 of 296 cases (22.3%) were excluded due to unusable capnography data. This resulted in a final study sample of 230 individual subjects with 1581 minutes of analyzed data. The median number of minutes of data analyzed per subject was six (range = 1–25). Demographics, event characteristics, and clinical outcomes are summarized in Table 1 for the 230 included subjects and for the 987 who were adult OHCA cases of presumed cardiac etiology who were excluded for insufficient corresponding CPR and capnography data. The cohort of excluded subjects had a lower proportion of cases who achieved ROSC (p = 0.01) and a higher proportion of subjects who survived (p = 0.043). Among the included cases, 30% had prehospital ROSC and 7.0% survived to hospital discharge. Among those with witnessed ventricular fibrillation (VF), 13.5% survived.

In Table 2, the $EtCO_2$ and CPR variables are stratified by the status of shockable initial rhythm, prehospital ROSC and survival. There were no significant differences in $EtCO_2$ between subjects with shockable and non-shockable initial rhythms. Those with prehospital ROSC had a higher $EtCO_2$ than those without ROSC [32.5 (5.3, 87.5) mmHg vs. 21.9 (6, 76.9) mmHg; p < 0.0001], but there was no difference in $EtCO_2$ between survivors and those who died. Additionally, there was a statistically significant difference in ventilation rates when subjects were stratified by initial rhythm and survival status; specifically, a lower ventilation rate was observed in subjects with a non-shockable initial rhythm and in those who did not survive to discharge.

In the regression models, log transformation was applied to $EtCO_2$ to achieve approximate normality. For reference, a box plot of the un-transformed raw data is shown in Figure 2. Scatter plots and locally-weighted polynomial regression suggested that there was an approximately-linear relationship between log $EtCO_2$ and the CPR variables, and the trend of log $EtCO_2$ over time was also approximately linear. Table 3 shows the results of linear mixed effect models fitted on the full dataset. $EtCO_2$ had a statistically significant positive association with CC depth when only time was adjusted for as a linear effect. A 10 mm increase in CC depth was associated with a 3.6% increase in $EtCO_2$. Additionally, an increase in ventilation rate by 10 breaths per minute (bpm) was associated with a 16.8% decrease in $EtCO_2$. After adjustment for CPR variables, a statistically significant positive association between $EtCO_2$ and CC depth, CC rate and CCRV was observed as was a statistically significant negative association between $EtCO_2$ and ventilation rate. The
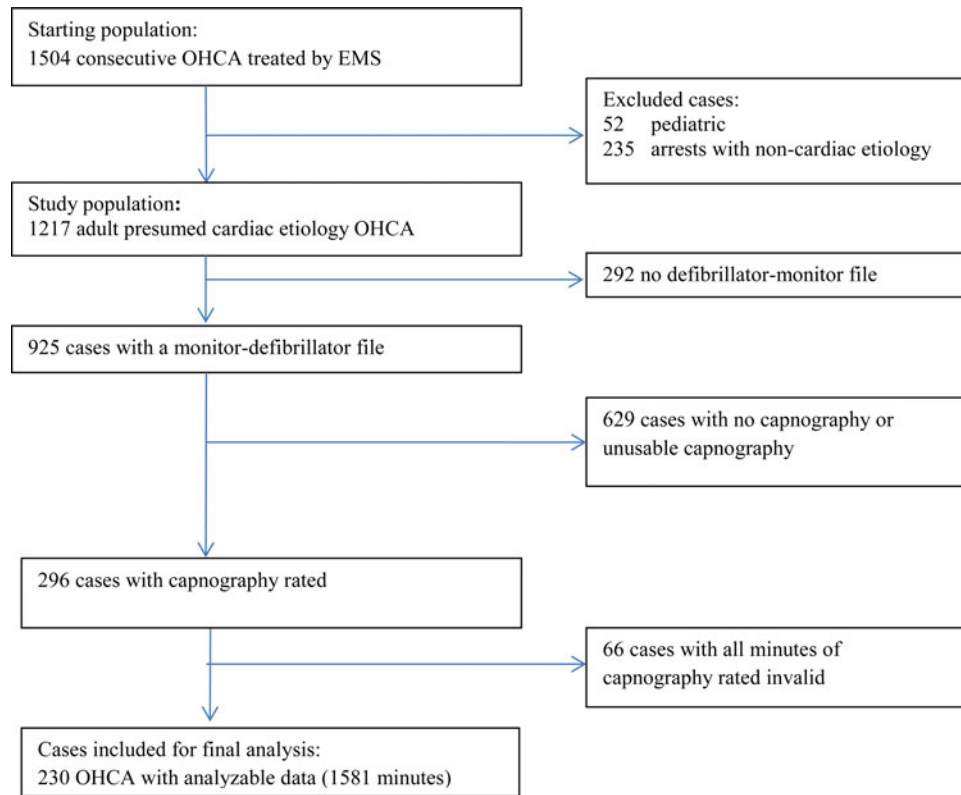
FIGURE 1. Study population inclusion/exclusion flow chart.

TABLE 1. Demographics, event characteristics, and clinical outcomes

		Included Cases N = 230	Excluded Cases N = 987	p-value*
Age		68.5 (22, 95) (n = 230)	67.0 (18, 99) (n = 967)	0.0647
Gender	Female	71 (30.9%)	348 (35.3%)	0.2178
	Male	159 (69.1%)	634 (64.2%)	
	Unknown	0 (0%)	5 (0.5%)	
Location of OHCA	Residential	153 (66.5%)	623 (63.1%)	0.5618
	Medical	37 (16.1%)	188 (19%)	
	Public	38 (16.5%)	160 (16.2%)	
	Unknown	2 (0.9%)	16 (1.6%)	
Witnessed	No	126 (54.8%)	507 (51.4%)	0.4372
	Seen	99 (43%)	336 (34%)	
	Heard	5 (2.2%)	15 (1.5%)	
	Unknown	0 (0%)	129 (13.1%)	
Shockable initial rhythm upon EMS arrival	Yes (V-fib/V-tach)	60 (26.1%)	219 (22.2%)	0.2979
	No (PEA, asystole, other)	170 (73.9%)	746 (75.6%)	
	Unknown	0 (0%)	22 (2.2%)	
ROSC	Yes	69 (30%)	206 (20.9%)	0.0153
	No	161 (70%)	721 (73%)	
	Unknown	0 (0%)	60 (6.1%)	
Survival to hospital discharge	Yes	16 (7%)	111 (11.2%)	0.0432
	No	214 (93%)	839 (85.0%)	
	Unknown	0 (0%)	37 (3.7%)	
Favorable Functional Outcome (CPC Score = 1 or 2)	Yes	13 (5.7%)	93 (9.4%)	0.0535
	No	217 (94.3%)	852 (86.3%)	
	Unknown	0 (0%)	42 (4.3%)	

CPC, cerebral performance category; IQR, interquartile range; OHCA, out of hospital cardiac arrest; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; V-fib, ventricular fibrillation; V-tach, ventricular tachycardia.
*Fisher's exact test for categorical variables and Wilcoxon rank-sum test for continuous variables; subjects with missing data (the unknown class) were excluded from the test.

TABLE 2. Summary of EtCO$_2$ and CPR quality variables among subjects included for analysis

| | Median (Range) | | |
	Shockable initial rhythm ($n = 60$)	Non-shockable initial rhythm ($n = 170$)	p-value*
EtCO$_2$ (mmHg)	24.3 (6.5, 55.6)	26 (5.3, 87.5)	0.093
CC Depth (mm)	53 (23.6, 82.6)	54.1 (15, 84.6)	0.3369
CC Rate (cpm)	102.6 (75.9, 179)	101 (78.4, 152.7)	0.0724
CCRV (mm/second)	32.9 (20.1, 42)	31.8 (8.5, 53.6)	0.6945
Ventilation Rate (bpm)	11.3 (4, 22.7)	8.2 (3.3, 25.3)	<0.0001
	ROSC ($n = 69$)	No ROSC ($n = 161$)	
EtCO$_2$ (mmHg)	32.5 (5.3, 87.5)	21.9 (6, 76.9)	0.0004
CC Depth (mm)	52.4 (15, 74.5)	54.4 (16.8, 84.6)	0.1711
CC Rate (cpm)	101 (75.9, 179)	101.4 (78.4, 161)	0.7003
CCRV (mm/second)	32.7 (8.5, 50.8)	31.7 (12.5, 53.6)	0.7709
Ventilation Rate (bpm)	9.8 (4, 25)	8.6 (3.3, 25.3)	0.0154
	Survival to discharge ($n = 16$)	No survival to discharge ($n = 214$)	
EtCO$_2$ (mmHg)	23.4 (8.5, 47.8)	25.3 (5.3, 87.5)	0.1436
CC Depth (mm)	54.1 (41.4, 71.1)	54 (15, 84.6)	0.5512
CC Rate (cpm)	100.4 (91.9, 179)	101.4 (75.9, 176.6)	0.3225
CCRV (mm/second)	33.3 (25.4, 45.2)	31.8 (8.5, 53.6)	0.4687
Ventilation Rate (bpm)	15.5 (9.7, 19.7)	8.7 (3.3, 25.3)	<0.0001

Bpm, breaths per minute; CC, chest compressions; CCRV, chest compression release velocity; cpm, compressions per minute; EtCO$_2$, end-tidal carbon dioxide; mm, millimeters.
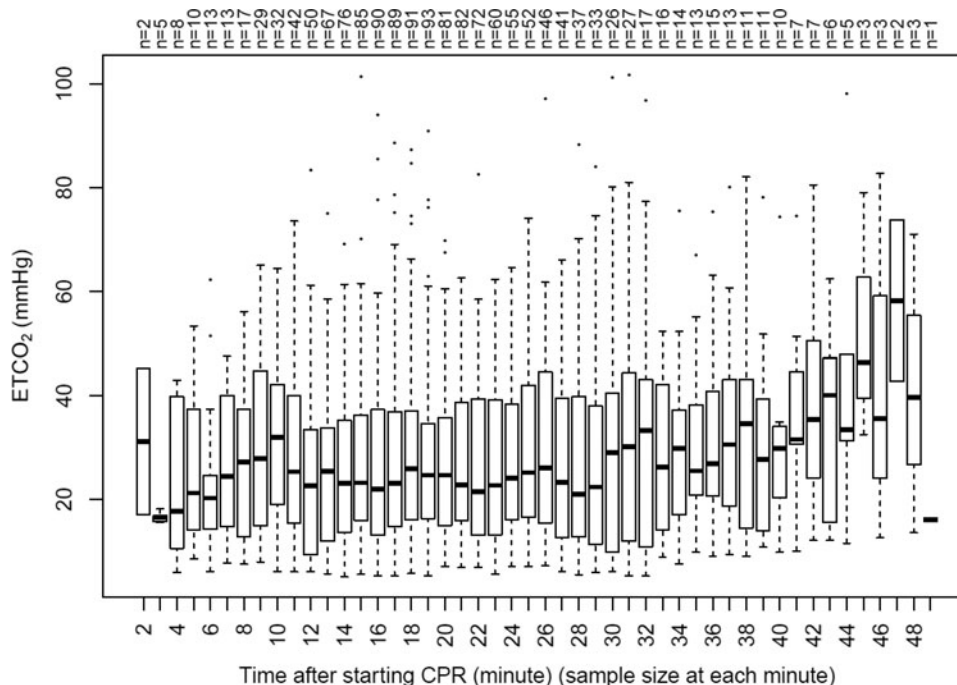*Wilcoxon rank-sum test.

FIGURE 2. Raw data box plot (prior to log transformation).

TABLE 3. Linear mixed effect models demonstrating association of EtCO$_2$ and CPR variables for all subjects included in final analysis ($n = 230$)

| | Unadjusted Analysis (adjusted for time only) | | | Adjusted Analysis (adjusted for time and other CPR variables[1]) | | |
	Effect (%)*	95% CI	p-value	Effect (%)*	95% CI	p-value
CC Depth (mm)	3.60	(1.9%, 5.4%)	0.0001	4.00	(2.3%, 5.8%)	<0.0001
CC Rate (cpm)	0.50	(−1%, 1.9%)	0.5343	1.70	(0.2%, 3.1%)	0.0222
CCRV (mm/second)	2.50	(−0.1%, 5.3%)	0.0597	2.80	(0.3%, 5.5%)	0.0314
Ventilation Rate (bpm)	−16.80	(−20%, −13.5%)	<0.0001	−17.40	(−20.5%, −14.1%)	<0.0001

Bpm, breaths per minute; CC, chest compressions; CCRV, chest compression release velocity; cpm, compressions per minute; EtCO$_2$, end-tidal carbon dioxide; mm, millimeters.
*Effect = Percentage change in EtCO$_2$ associated with a 10-unit increase in each CPR variable.
[1]Other CPR variables = CC depth, CC rate, CCRV and ventilation rate
(note: CC depth and CCRV were no included in same model due to co-linearity.)

sensitivity analysis gave very similar results when each minute was allowed to have a separate effect on $EtCO_2$.

Additional stratified analyses were conducted separately for subjects according to shockable vs. non-shockable initial rhythms (Table 4) and presence or absence of prehospital ROSC (Table 5). Those with non-shockable initial rhythms showed a statistically significant positive association between $EtCO_2$ and CC depth, while, in those with initial shockable rhythms, there was a statistically significant association between $EtCO_2$ and both CC depth and CCRV. For those patients not achieving prehospital ROSC, a statistically significant association existed between $EtCO_2$ and each of the CPR variables. This was not true for those who did achieve prehospital ROSC. We did not perform an analysis stratified by survival status given the small number of survivors.

DISCUSSION

CPR is the key to successful cardiac resuscitation and maximizing blood flow during CPR is believed to be one of the most significant factors related to outcome from cardiac arrest.[2,16,17] Guidelines defining "optimal CPR" have been established based upon mean data from large observational studies that have associated various CPR metrics with ROSC and survival.[8,10,18–22] Due to the wide variability in patient anatomy and physiology, the concept that CPR might ultimately be tailored to individual patients and measured by their physiologic response to CPR, rather than being guided by rigid CPR targets (e.g., CC depth >50 mm), is attractive. In fact, current guidelines recommend that waveform capnography be carried out during resuscitation to assess forward blood flow and monitor CPR quality.[2,23]

For several decades it has been known that higher levels of $EtCO_2$ are associated with successful cardiac resuscitation in animal models.[24–26] There are three major determinants of $EtCO_2$: tissue CO_2 production, pulmonary blood flow, and alveolar ventilation. Multiple laboratory studies have confirmed that during periods of acute decreases in cardiac output, such as during cardiac arrest, pulmonary blood flow becomes the major determinant of $EtCO_2$.[27,28] In animal models, $EtCO_2$ has been found to correlate with coronary and cerebral perfusion pressures during CPR.[25,29] Recent clinical studies have also demonstrated a positive correlation between $EtCO_2$ levels and outcomes from cardiac arrest.[4,6,30–32] Specifically, patients with higher $EtCO_2$ levels have a greater likelihood of obtaining ROSC, sustaining ROSC, and surviving to hospital discharge.[5,31–34] Additionally, multiple studies have evaluated the potential of $EtCO_2$ to predict mortality.[35–37] It has been reported that an $EtCO_2$ level of 15 mmHg or less, measured 20

TABLE 4. Association of $EtCO_2$ and CPR variables stratified by initial rhythm (shockable vs. non-shockable)

		Unadjusted Analysis (adjusted for time only)			Adjusted Analysis (adjusted for time and other CPR variables[1])		
		Effect (%)*	95% CI	p-value	Effect (%)*	95% CI	p-value
CC Depth (mm)	Shockable[2] (n = 60)	5.60	(2.2%, 9%)	0.0010	6.50	(3.1%, 10%)	0.0002
	Non-shockable[3] (n = 170)	2.90	(0.9%, 5.1%)	0.0055	3.20	(1.1%, 5.2%)	0.0021
CC Rate (cpm)	Shockable (n = 60)	0.50	(−1.6%, 2.7%)	0.6471	1.90	(−0.3%, 4.2%)	0.0911
	Non-shockable (n = 170)	0.50	(−1.4%, 2.5%)	0.5822	1.70	(−0.2%, 3.6%)	0.0777
CCRV (mm/ second)	Shockable (n = 60)	6.40	(1.2%, 11.9%)	0.0150	7.20	(2%, 12.6%)	0.0062
	Non-shockable (n = 170)	1.30	(−1.7%, 4.5%)	0.4001	1.40	(−1.6%, 4.4%)	0.3762
Ventilation Rate (bpm)	Shockable (n = 60)	−13.90	(−19.9%, −7.6%)	< 0.0001	−14.50	(−20.4%, −8.3%)	< 0.0001
	Non-shockable (n = 170)	−18.10	(−21.8%, −14.1%)	< 0.0001	−18.60	(−22.4%, −14.8%)	< 0.0001

Bpm, breaths per minute; CC, chest compressions; CCRV, chest compression release velocity; cpm, compressions per minute; $EtCO_2$, end-tidal carbon dioxide; mm, millimeters.
*Effect = Percentage change in $EtCO_2$ associated with a 10-unit increase in each CPR variable.
[1]Other CPR variables = CC depth, CC rate, CCRV and ventilation rate
(note: CC depth and CCRV were no included in same model due to co-linearity).
[2]Shockable = initial rhythm recorded by EMS to be either ventricular fibrillation or ventricular tachycardia.
[3]Non-shockable = initial rhythm recorded by EMS to be asystole, PEA or other.

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TABLE 5. Association of $EtCO_2$ and CPR variables stratified by prehospital ROSC status

		Unadjusted Analysis (adjusted for time only)			Adjusted Analysis (adjusted for time and other CPR variables[1])		
		Effect (%)*	95% CI	p-value	Effect (%)*	95% CI	p-value
CC Depth (mm)	ROSC (n = 69)	1.80	(−1.6%, 5.4%)	0.2971	1.70	(−1.7%, 5.2%)	0.3274
	NO ROSC (n = 161)	4.40	(2.4%, 6.5%)	< 0.0001	5.10	(3.1%, 7.2%)	< 0.0001
CC Rate (cpm)	ROSC (n = 69)	−0.30	(−3.3%, 2.8%)	0.8423	0	(−3.3%, 3.1%)	0.9853
	NO ROSC (n = 161)	0.70	(−0.9%, 2.3%)	0.3882	2.30	(0.7%, 3.9%)	0.0051
CCRV (mm/ second)	ROSC (n = 69)	1.40	(−3.5%, 6.5%)	0.5789	1.30	(−3.5%, 6.3%)	0.6007
	NO ROSC (n = 161)	3.10	(0%, 6.3%)	0.0498	3.60	(0.6%, 6.8%)	0.0194
Ventilation Rate (bpm)	ROSC (n = 69)	−13.60	(−20%, −6.8%)	0.0002	−13.50	(−19.9%, −6.7%)	0.0002
	NO ROSC (n = 161)	−18.20	(−21.8%, −14.4%)	< 0.0001	−19.20	(−22.7%, −15.5%)	< 0.0001

Bpm, breaths per minute; CC, chest compressions; CCRV, chest compression release velocity; cpm, compressions per minute; $EtCO_2$, end-tidal carbon dioxide; mm, millimeters.
*Effect = Percentage change in $EtCO_2$ associated with a 10-unit increase in each CPR variable.
[1] Other CPR variables = CC depth, CC rate, CCRV and ventilation rate
(note: CC depth and CCRV were no included in same model due to co-linearity).

minutes after the initiation of advanced cardiac life support, can accurately predict death in patients with non-shockable initial rhythms suffering from cardiac arrest.[35]

In this study, $EtCO_2$ was significantly associated with CC depth, CC rate and CCRV after adjusting for the other CPR variables. Specifically, a 10 mm increase in CC depth was associated with a 4.0% increase in $EtCO_2$, a 10 CC/minute increase in compression rate was associated with a 1.7% increase in $EtCO_2$, and a 10 mm/second increase in CCRV was associated with a 2.8% increase in $EtCO_2$. In a subgroup analysis based on ROSC status, similar associations were found in the non-ROSC group, but were not demonstrated in the ROSC group. The reasons for this finding are unclear, but could reflect the unintentional inclusion of minutes with ROSC in our analysis. Chest compressions likely have a limited effect on $EtCO_2$ when there is underlying ROSC.

Sheak recently published a cohort study (583 adult subjects with 227 in-hospital cardiac arrests (IHCA) and 356 OHCA) aimed at quantifying the relationship between $EtCO_2$ and CPR characteristics.[7] As with the current study, they found a statistically significant association between deeper CCs and higher $EtCO_2$ values (for every 10 mm increase in depth, $EtCO_2$ rose by 1.3 mmHg; $p < .001$).[7] While we reported a significant association between CC rate and $EtCO_2$ ($p = 0.04$), Sheak did not identify this association.[7] There are several fundamental differences between Sheak's study and ours. Most significantly, our study included only *out-of-hospital* arrests of presumed cardiac etiology. This distinction is important as the differences between OHCA and IHCA (e.g., inciting etiologies, patient populations, and time intervals to initiating CPR, advanced airway and $EtCO_2$ measurement) have been shown to impact $EtCO_2$ levels.[3,31,34] In addition, we evaluated CCRV as a CPR quality metric. Finally, as the Linear Mixed Effect Model requires a normally distributed outcome variable and the $EtCO_2$ levels were right-skewed, we applied a log transformation that produced a best-fit for evaluating these results.

While both Sheak and this analysis demonstrated positive associations between $EtCO_2$ and several CC variables, it is important to note that the observed effect sizes are relatively modest. For instance, at the mean $EtCO_2$ level of 25 mmHg, an effect size of 4% equates to only a 1 mmHg change in $EtCO_2$. Additionally, the effect sizes between $EtCO_2$ and the CC variables are much smaller than between ventilation rate and $EtCO_2$. Unless ventilation is carefully controlled, variations in ventilation may further obscure interpretations of CC quality. Furthermore, there is wide variability in $EtCO_2$ values due to the technical challenges inherent to capnography monitoring (e.g., waveform artifact, system leaks). Finally, the use of $EtCO_2$ to monitor CPR quality only applies to

intubated patients with ongoing CPR. Many of the exclusions in Figure 1 are a result of this inherent limitation. Thus, while we found statistically significant associations between $EtCO_2$ and CPR metrics, several issues limit the clinical utility of $EtCO_2$ as a real-time guide to CPR quality in the field.

LIMITATIONS

While this study demonstrated an independent and statistically significant association between $EtCO_2$ and CPR quality variables, the observational design does not allow a specific determination of causality. Additionally, other factors not included in this analysis have the potential to affect our results (e.g., epinephrine administration, metabolic derangements, variation in minute ventilation). In this study we measured ventilation rates, but were not able to reliably measure ventilation volumes (ventilation rates were identified by capnography waveforms, but variation in ventilation volumes were not accounted for). Alveolar ventilation (one of the 3 key components of $EtCO_2$) is determined by rate AND volume of applied ventilation and without a precise volumetric measurement, we were unable to fully assess this confounder. Another limitation is that, while we rigorously reviewed files for ROSC periods, it is possible that periods with ROSC and ongoing CCs were included in the analysis.

The potential impact of $EtCO_2$ monitoring to guide CPR quality is limited by the fact that just 296/925 (32%) cases with CPR quality data had adequate corresponding capnography data. Additionally, as is common in prehospital studies, there were episodes of missing data. To help mitigate the issue of missing data and potential bias, we present a comparison between included and excluded subjects in Table 1. The EMS agencies in this study followed a resuscitation protocol focusing on high quality CPR and delayed advanced airway placement for the first 6–8 minutes of resuscitation.[8] As such, the capnography data does not reflect the early minutes of CPR and results may be different from other EMS systems.

CONCLUSION

In this observational study, after controlling for other CPR variables, increases in chest compression depth, rate and release velocity were independently associated with statistically significant increases in $EtCO_2$ levels during CPR. The small effect sizes, however, draw into the question the clinical utility of $EtCO_2$ to guide CPR performance without additional CPR quality or physiologic monitoring. Further research is needed to determine if real-time $EtCO_2$ can be utilized to effectively improve prehospital CPR quality and patient outcomes.

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