A Pilot Study of End-Tidal Carbon Dioxide in Prediction of Inhospital Cardiac Arrests

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Objectives: A validated means to predict inhospital cardiac arrest is lacking. The purpose of this study was to evaluate the changes in end-tidal carbon dioxide, as it correlates with the progression to inhospital cardiac arrest in ICU patients.

Design, Setting, and Patients: Single-center, retrospective cohort study of mechanically ventilated ICU patients (age > 18 yr old) having inhospital cardiac arrest with advanced cardiac life support and continuous end-tidal carbon dioxide monitoring at a single academic center from 2014 to 2017. Demographics, clinical variables, and outcomes were collected. End-tidal carbon dioxide was collected from 5 to 2,880 minutes before inhospital cardiac arrest. Data were analyzed using descriptive statistics, and model estimates were generated using a repeated-measures categorical model with restricted maximum likelihood estimation and fully specified (autoregressive) covariance to assess the effect of time on changes in end-tidal carbon dioxide.

Measurements and Main Results: A total of 788 patients were identified and 104 met inclusion criteria, where 62% were male with an average age of 58.5 years. Seventy-four percent required vasopressors and 72% experienced pulseless electrical activity. Mean end-tidal carbon dioxide 5 minutes prior to inhospital cardiac arrest was significantly lower than all evaluated time points except 180 minutes ($p < 0.05$). One patient survived to hospital discharge. In multivariate logistic regression modeling for return of spontaneous circulation, a greater change in the prearrest end-tidal carbon dioxide maximum to prearrest end-tidal carbon dioxide minimum was associated with a decreased likelihood of return of spontaneous circulation (odds ratio 0.903; 95% CI, 0.832–0.979; $p = 0.014$). Additionally, a change from prearrest end-tidal carbon dioxide maximum to prearrest end-tidal carbon dioxide minimum greater than 17 mm Hg was associated with a decreased likelihood of return of spontaneous circulation and odds ratio 0.150; 95% CI, 0.036–0.66; $p = 0.012$).

Conclusions: Mean end-tidal carbon dioxide is significantly lower immediately before inhospital cardiac arrest. The statistical and clinical significance of end-tidal carbon dioxide may highlight its utility for predicting inhospital cardiac arrest in ICU patients. Comparison analysis and modeling explorations in a larger cohort are needed.

Key Words: cardiology; critical care; end-tidal carbon dioxide; inhospital cardiac arrest; intensive care unit

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Inhospital cardiac arrest (IHCA) affects almost 300,000 adults yearly, resulting in poor clinical outcomes (1, 2). Early prediction is, therefore, paramount to identify patients at risk for IHCA. Early identification may help expedite life-saving medical interventions and improve outcomes. Currently, there is a lack of data validating any one tool or parameter that could predict an IHCA. Although standard vital signs (e.g., heart rate [HR], blood pressure, respiratory rate, and oxygen saturation) have been monitored and documented in critically ill patients for many decades, end-tidal carbon dioxide ($ETCO_2$) monitoring has become more routine in critically ill patients over the last 10–20 years. $ETCO_2$ is a noninvasive measurement of exhaled carbon dioxide (CO_2), which may be a potential clinical parameter useful for IHCA prediction (3). Under normal conditions, $ETCO_2$ is a noninvasive estimate of alveolar ventilation status, as it correlates with $Paco_2$ (3–5). An increased gradient between $ETCO_2$ and $Paco_2$ can be an indication of dead-space ventilation, such as atelectasis, or changes to lung perfusion, such as pulmonary embolism. Furthermore, data suggest there is a correlation between $ETCO_2$ and cardiac output, which may lend utility in forecasting cardiac

arrest (5, 6). In recent analyses, investigators observed a significant association between $ETCO_2$ concentration and inhospital mortality in emergency department patients with suspected sepsis across a range of disease severity (7). Additionally, it was found that $ETCO_2$ inversely correlates with lactate levels and could be used to aid diagnosis and early detection of sepsis. We hypothesize that acute changes of $ETCO_2$ correlate with the development of IHCA in ICU patients. Thus, the primary objective of this study was to evaluate changes in $ETCO_2$ over time, as it correlates with the progression to IHCA in ICU patients.

MATERIALS AND METHODS

This was a retrospective, single-center, Institutional Review Board-approved cohort study. Patients screened for enrollment in the study were those having IHCA at a single academic medical center from January 1, 2014, to December 12, 2017. Inclusion criteria were patient age greater than or equal to 18 years with a documented IHCA in the ICU for whom advanced cardiac life support (ACLS) was performed. Patients were excluded if they had orders to withhold resuscitation efforts or had a lack of documented continuous $ETCO_2$ 1 hour prior to IHCA. Demographics including past medical history, arrest- and resuscitation-related variables, clinical variables (sodium, potassium, chloride, bicarbonate, blood urea nitrogen [BUN], serum creatinine, glucose, calcium, phosphate, magnesium, creatinine, estimated creatinine clearance, lactic acid, and arterial blood gas: pH, Pco_2, and Po_2), vital signs, $ETCO_2$ values at multiple time points, return of spontaneous circulation (ROSC—defined by a sustained heart rhythm, rate and blood pressure leading to ability to stop resuscitation efforts), mortality (defined as being alive at the end of noted hospitalization), and disposition (positive discharge disposition being defined as being alive and discharged to home, skilled nursing facility, long-term care facility, or acute rehabilitation) were collected. The primary outcome of the study was to evaluate the trend of $ETCO_2$ over time leading up to the IHCA. Secondary outcomes included identifying clinical and $ETCO_2$ parameters that were associated with disposition and outcomes in IHCA. Data points were manually collected by two authors in an effort to ensure consistency of variable extraction.

Statistical Plan

The primary outcome was analyzed using model estimates generated by using a repeated-measures categorical model with restricted maximum likelihood estimation and fully specified (autoregressive) covariance to assess the effect of time on changes in $ETCO_2$. This model was chosen to minimize bias introduced from missing $ETCO_2$ values in the cohort. Univariate analyses were performed for correlations between independent variables and dependent secondary outcomes of ROSC, positive discharge disposition, and survival. Variables resulting in a

p value of less than 0.1 via univariate analysis were included in multivariate logistic regression modeling to investigate factors associated with the development of these events. Variables demonstrating collinearity were not included in multivariate modeling

RESULTS

Of the 788 patients with an IHCA during the specified time period, 104 met the inclusion criteria for this study. The sole exclusion reason was a lack of $ETCO_2$ monitoring in the 1 hour prior to IHCA (**Fig. 1**). The population was 62% male and 53% Black, with an average age of 58.5 years (**Table 1**). The patients included had multiple comorbidities including coronary artery disease, arrhythmias, and chronic kidney disease of 85%, 43%, and 25%, respectively. All patients were mechanically ventilated and 74% required vasopressors prior to the IHCA. The predominant cardiac "rhythm" during the IHCA was pulseless electrical activity (PEA) followed by asystole. The average baseline laboratory values were all within normal limits except for elevated serum creatinine (2.8 mg/dL), BUN (39.8 mg/dL), lactate (6.6 mmol/L), and decreased serum calcium (7.9 mg/dL) and pH (7.24). The mean $ETCO_2$ value 5 minutes prior to the onset of the IHCA was significantly lower than the measurements at all other time points in this population except at 180 minutes (**Fig. 2**, **A** and **B**; $p < 0.05$). When evaluating other vital signs, only HR also followed a similar trend, with the 5-minute prearrest HR being statistically lower than all other measured time points (**Table 2** and **Fig. 3**). Mean arterial pressure and respiratory rate did not follow this trend (Table 2 and Fig. 3). Overall, outcomes were poor in our cohort with four patients surviving to discharge and only one patient with a positive discharge disposition (**Table 3**). In multivariate logistic regression modeling for ROSC, a greater change in the prearrest $ETCO_2$ maximum to prearrest $ETCO_2$ minimum was associated with a decreased likelihood of ROSC (odds ratio [OR] 0.903; 95% CI, 0.832–0.979; $p = 0.014$). Additionally, a change from prearrest $ETCO_2$ maximum to prearrest $ETCO_2$ minimum greater than 17 mm Hg was associated with a decreased likelihood of ROSC (OR 0.150; 95% CI, 0.036–0.66; $p = 0.012$). No variables were associated with disposition and survival in regression modeling.
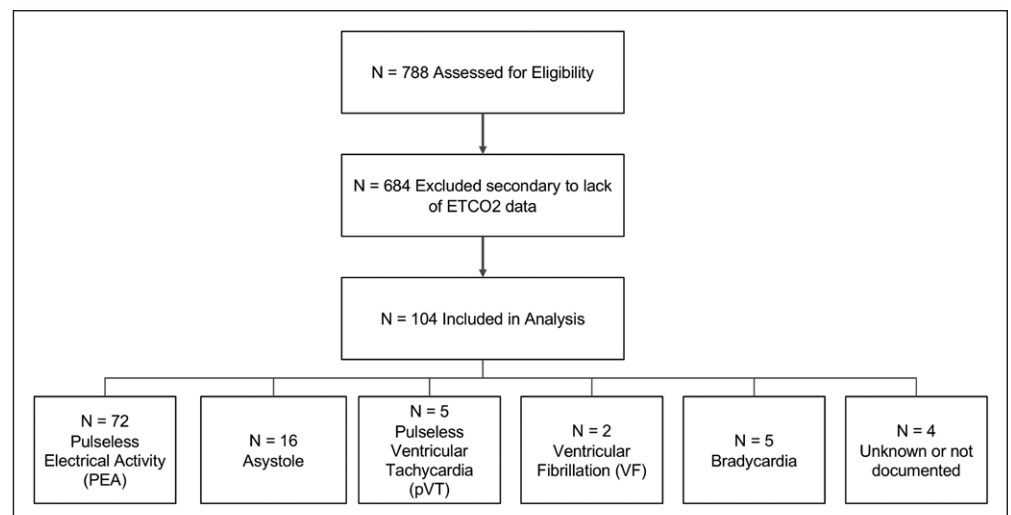

Figure 1. Consolidated Standards of Reporting Trials diagram for inclusion. $ETCO_2$ = end-tidal carbon dioxide.

TABLE 1. Baseline Characteristics

Demographics	n = 104
Age, yr, average ± SD	58.5 ± 15.2
Race	
American Indian, n (%)	1 (1)
Asian, n (%)	3 (2.9)
Black, n (%)	53 (51)
White, n (%)	19 (18.3)
Hispanic, n (%)	1 (1)
Not reported, n (%)	27 (26)
Male, n (%)	62 (59.6)
Unit	
Medical ICU, n (%)	88 (84.6)
Surgical ICU, n (%)	6 (5.8)
NeuroICU, n (%)	10 (9.6)
PMH coronary artery disease, n (%)	85 (81.7)
PMH arrhythmia, n (%)	43 (41.3)
PMH CKD, n (%)	25 (24)
Stage of CKD	
Stage 1, n (%)	0 (0)
Stage 2, n (%)	1 (1)
Stage 3, n (%)	3 (2.9)
Stage 4, n (%)	0 (20.2)
Stage 5, n (%)	21 (24)
End-stage renal disease requiring intermittent hemodialysis, n (%)	22 (21.2)
Mechanically ventilated, n (%)	104 (100)
Ongoing sepsis, n (%)	85 (81.7)
Vasopressors usage, n (%)	74 (71.2)
Median number vascular access sites, n (interquartile range)	3 (2–4)
IV line(s), n (%)	104 (100)
Intraosseus line(s), n (%)	3 (2.9)
Central line(s), n (%)	94 (90.4)
Peripheral line(s), n (%)	79 (76)
Laboratory Values	
pH, average ± SD	7.24 ± 0.18
P_{CO_2}, mm Hg, average ± SD	38.2 ± 12.0
P_{O_2}, mm Hg average ± SD	103.3 ± 53.3
Sodium, mmol/L, average ± SD	138.5 ± 6.0

(*Continued*)

TABLE 1. (*Continued*). Baseline Characteristics

Demographics	n = 104
Potassium, mmol/L, average ± SD	4.7 ± 1.1
Chloride, mmol/L, average ± SD	105.5 ± 6.9
Calcium, mg/dL, average ± SD	7.9 ± 0.9
Magnesium, mg/dL, average ± SD	2.2 ± 0.4
Phosphate, mg/dL, average ± SD	5.6 ± 2.4
Blood urea nitrogen, mg/dL, average ± SD	39.8 ± 27.5
Serum creatinine, mg/dL, average ± SD	2.8 ± 2.1
Creatinine clearance (Cockraft and Gault), mL/min, average ± SD	35.9 ± 29.8
Glucose, mg/dL, average ± SD	139.8 ± 60.6
Lactate, mmol/L, average ± SD	6.6 ± 6.0
Glasgow Coma Scale, n (%)	
Severe (3–8)	66 (63.5)
Moderate (9–13)	25 (24)
Mild (14–15)	5 (4.8)
Missing score	8 (7.7)

CKD = chronic kidney disease, PMH = past medical history.
Demographic data is presented in average ± SD, median (interquartile range), n (%) as statistically appropriate.

DISCUSSION

We sought to determine the association between $ETCO_2$ levels over time and progression to IHCA in ICU patients. This retrospective cohort study demonstrates an inverse relationship between $ETCO_2$ levels and the time leading up to IHCA. With the exception of 180 minutes, the mean $ETCO_2$ level 5 minutes prior to the onset of IHCA was significantly lower than all other time points. Multivariate logistic regression for ROSC indicates that the absolute change in prearrest $ETCO_{2-MAX}$ to prearrest $ETCO_{2-MIN}$ and change from prearrest $ETCO_{2-MAX}$ to prearrest $ETCO_{2-MIN}$ greater than 17 mm Hg were associated with a decreased likelihood of achieving ROSC.

CO_2 is a product of cellular respiration, which is removed during exhalation. $ETCO_2$ is the partial pressure of the exhaled CO_2 at the end of each exhaled breath, and changes in $ETCO_2$ are related to changes in the production of CO_2, alveolar gas exchange, lung perfusion, and cardiac output (8). Measurement of $ETCO_2$ can provide a noninvasive estimate of cardiac output and organ perfusion during cardiac arrest, and therefore can be used to predict ROSC and future cardiac arrest (8).

The majority of studies using $ETCO_2$ have shown utility during cardiopulmonary resuscitation (CPR) (9). Levine et al (10) in 1997 conducted a study in 150 out-of-hospital cardiac arrest (OHCA) patients and found that all patients that had an $ETCO_2$ of 10 mm Hg or less 20 minutes after the start of ACLS did not survive. Conversely, all patients that had an $ETCO_2$ above this threshold of 10 mm Hg experienced ROSC (10). A similar study by Grmec and Klemen (11) prospectively analyzed the $ETCO_2$
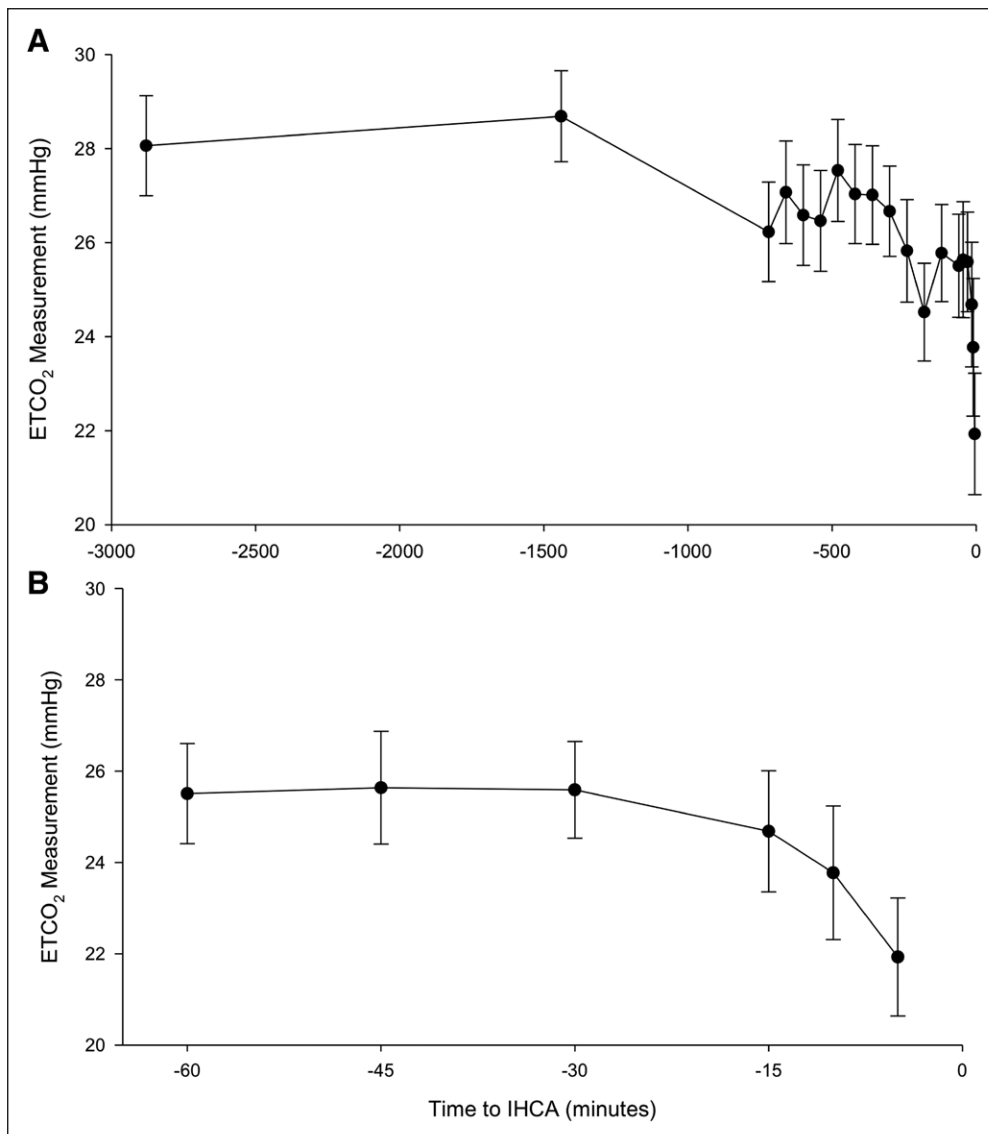
Figure 2. Relationship of end-tidal carbon dioxide ($ETCO_2$) versus time leading to inhospital cardiac arrest (IHCA). **A**, Average (SE) $ETCO_2$ values versus time leading up to IHCA. $p < 0.05$ for all times points except T-180 compared with reference T-5 minutes before IHCA. **B**, Average (SE) $ETCO_2$ values versus time of T-60 minutes leading to the IHCA. $p < 0.05$ for all times points compared with reference T-5 minutes before IHCA.

impending loss of spontaneous circulation as body systems begin to fail. Our study supports this hypothesis, and the high proportion of PEA arrest in our cohort is suggestive of significant perfusion abnormalities, such as myocardial infarction and pulmonary embolism, as the potential cause of IHCA. Additionally, in these subjects on volume-controlled mechanical ventilation, the lack of significant alterations in respiratory rate in the time leading up to arrest suggests that $ETCO_2$ was not altered by changes in minute ventilation.

Future direction will be to evaluate patients with and without IHCA in a broad ICU population to compare trends of $ETCO_2$ throughout ICU stay. Once validated, $ETCO_2$ parameters can be developed to predict potentially an impending IHCA by using a change in baseline $ETCO_2$ or identify absolute minimums that lead to impending IHCA. Automated continuous $ETCO_2$ monitoring combined with machine-learning–based algorithms could enable early recognition of changes in perfusion allowing earlier treatment or prevention of IHCAs and possibly decreasing mortality and improving outcomes (14). A model of machine learning can then be used to predict IHCA similar to those developed to predict deterioration in other critical care disease processes (15, 16). By using $ETCO_2$ and this type of predictive analytics, warning of impending cardiorespiratory deterioration can save time and patient lives by moving from a reactive response to deterioration into a proactive treatment of impending distress (14, 17).

There were several limitations to this study. Due to the inability to automate data extraction from the electronic medical record (EMR), data extraction was a manual process. In an effort to ensure the accurate extraction of information, two research personnel were responsible for the majority of data collection. Moreover, pertinent variables that may confound outcomes, like quality of CPR, were not collected. The quality of CPR is known to affect the outcomes of cardiac arrest (18). These data may not have been available for every situation due to the lack of availability of the technology to capture the data. Additionally, at our institution, it is not recorded in the EMR. To such a degree, it would be a confounding variable to interpreting outcomes of our analysis. Additionally, due to the retrospective nature of the research, some data points were missing from the subjects included in the

levels in 139 OHCA patients and observed that every patient with an $ETCO_2$ below 10 mm Hg failed to achieve ROSC, whereas every patient above this level did. Although these studies consisted of OHCA patients and focused on the prognostic value of $ETCO_2$ rather than its predictive value, there appears to be a relationship among $ETCO_2$, return of innate cardiac output, and ROSC.

It has been found that during experimental CPR, $ETCO_2$ has shown a significant positive correlation with cardiac index and with coronary and cerebral perfusion pressures (8). In a similar fashion, Falk et al (12) observed that decreases in expired $ETCO_2$ is correlated with decreased cardiac output and pulmonary blood flow during circulatory arrest. Due to the relationship between $ETCO_2$ and perfusion, the association between $ETCO_2$ values and mortality is thought to be related to its use as a marker for inadequate ventilation, metabolic disturbances, or poor perfusion (7, 13). Therefore, a rapid decrease in $ETCO_2$ could be a marker of

TABLE 2. Vital Signs Leading up to Inhospital Cardiac Arrest

Time Point (T-min)	Average Heart Rate ± SD (Beats/min)	p	Average Mean Arterial Pressure ± SD (mm Hg)	p	Average Respiratory Rate ± SD (Breaths/min)	p
5	79.5 ± 27.7		60.8 ± 23.6		25.2 ± 13.1	
10	87.6 ± 28.9	**0.009**	60.4 ± 18	0.879	24.1 ± 6.6	0.184
20	88.8 ± 27	**0.039**	64 ± 17.1	0.248	23.9 ± 6.9	0.957
30	94.9 ± 25.2	**< 0.001**	64.5 ± 16.1	0.349	24.5 ± 6.8	0.309
45	95.6 ± 26	**0.001**	67.1 ± 18.7	0.134	25.3 ± 7.1	0.580
60	96.7 ± 22.8	**< 0.001**	69.3 ± 17.6	0.094	26.2 ± 7.4	0.146

All time points were compared with T-5 minutes for analysis. Boldface values were statistically significant.

analysis. This could be attributed to a variety of reasons, one of which can be credited to patient acuity; higher patient acuity requires increased monitoring and thus increased documentation which may have been incomplete. Additionally, patients varied in acuity prior to IHCA; thus, the availability of hourly variables may not have been required as a part of documentation in the lesser acuity patients. The repeated-measures linear models estimate, via direct likelihood, offer unbiased estimates under missing at random (MAR) assumptions. The MAR assumptions assume that data are MAR or the missingness is covariate-dependent, and thus limits the bias of missing data points. Though this is a limitation, the majority of variables that directly influence

$ETCO_2$ trending were collected. Furthermore, select few of the $ETCO_2$ data were not collected precisely on the hour. This can again be related to patient situations and a focus on real-time documentation. This led to the inability to evaluate precise hour-related features of $ETCO_2$ changes leading up to IHCA. This was the minority of cases, and there was a threshold set a priori of allowable time away from a given hour time point to be included in the data set. The current study did not include subjects that did not progress to IHCA, but rather each subject served as their own internal control with little variability in $ETCO_2$ noted in any given subject. It remains unknown if significant variability of $ETCO_2$ would be identified in subjects that did not progress to
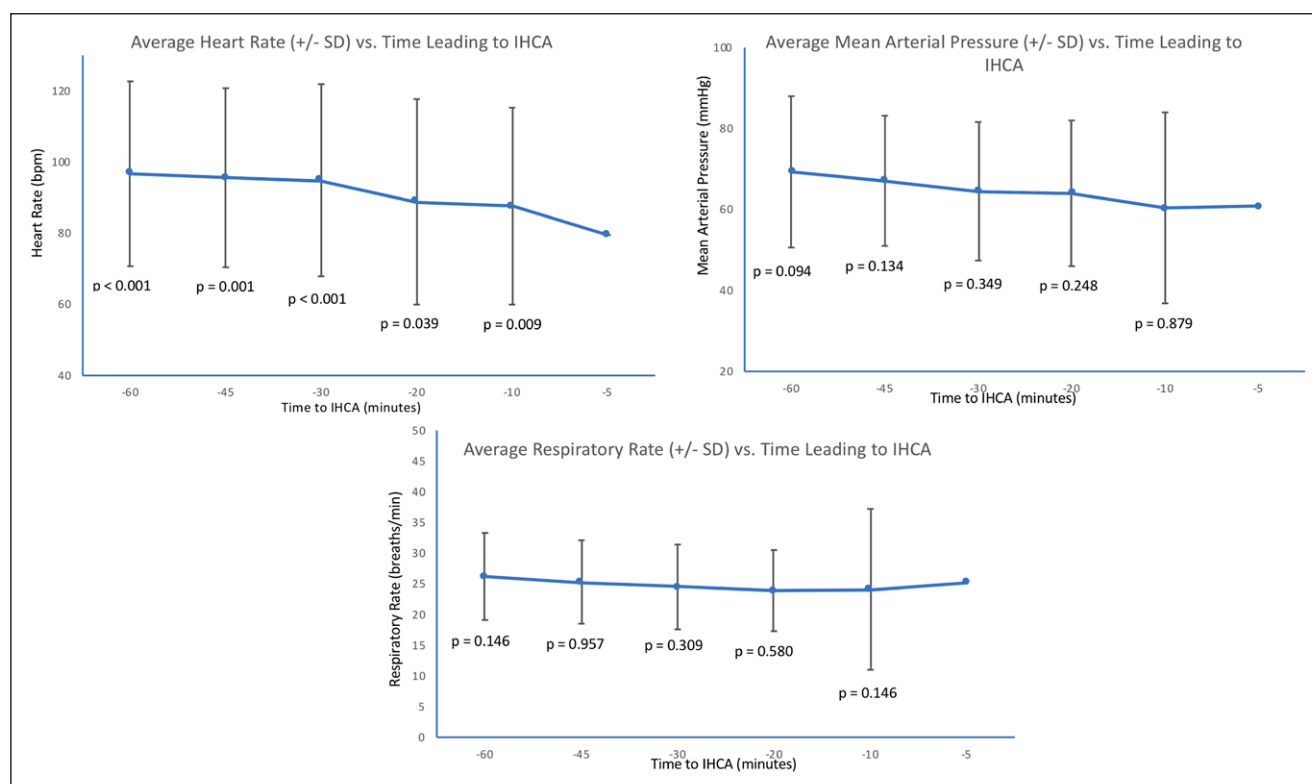

Figure 3. Average (SD) vital signs versus time leading to inhospital cardiac arrest. The reference time point for each comparison was time = T-5 minutes. IHCA = inhospital cardiac arrest.

TABLE 3. Cardiac Arrest Variables and Outcomes

Arrest- or Outcome-Related Variable	$n = 104$
Duration of resuscitation, min, average ± SD	15.0 ± 12.3
Presenting rhythm	
Asystole, n (%)	16 (15.4)
Pulseless electrical activity, n (%)	72 (69.2)
Pulseless ventricular tachycardia n (%)	5 (4.8)
Ventricular fibrillation, n (%)	2 (1.9)
Bradycardia, n (%)	5 (4.8)
Unknown or not documented, n (%)	4 (3.8)
Return of spontaneous circulation, n (%)	67 (64.4)
Survival to hospital discharge, n (%)	4 (3.8)
Positive discharge disposition, n (%)	1 (0.96)

IHCA, yet the goal of using these changes as an early warning of impending IHCA would have little impact in subjects that do not progress to IHCA. Additionally, given that all of our cohort was mechanically ventilated, there is limited generalizability to non-mechanically ventilated patients. Finally, a major limitation is the overall lack of technology to identify clinically significant trends and changes in vital signs and $ETCO_2$. Clinical significance varies and is dependent on the patient's baseline status and acuity. Although an emerging field, further research and technological advancements in artificial intelligence, machine learning, and predictive analytics are needed in order to capture individualized, patient specific trends in $ETCO_2$.

CONCLUSIONS

This work suggests a role for decreases in $ETCO_2$ being used as an early-warning system for IHCA. Mean $ETCO_2$ was significantly lower immediately prior to IHCA than nearly all other comparison time points in the preceding 48 hours. Additionally, the change in prearrest $ETCO_2$ of greater than 17 mm Hg was associated with a poor response to CPR. The resulting statistical and clinical significance of $ETCO_2$ trends in this target population indicates that this technology can have other meaningful uses in the critically ill, such as in predicting future IHCA, shown here. This pilot study confirms the need for comparison analysis and modeling explorations in a larger cohort to expand the utility and importance of continuous $ETCO_2$ monitoring.

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