Artificial Intelligence for End Tidal Capnography Guided Resuscitation: A Conceptual Framework

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Abstract

Artificial Intelligence (AI) and machine learning have advanced healthcare by defining relationships in complex conditions. Out-of-hospital cardiac arrest (OHCA) is a medically complex condition with several etiologies. Survival for OHCA has remained static at 10% for decades in the United States. Treatment of OHCA requires the coordination of numerous interventions, including the delivery of multiple medications. Current resuscitation algorithms follow a single strict pathway, regardless of fluctuating cardiac physiology. OHCA resuscitation requires a real-time biomarker that can guide interventions to improve outcomes. End tidal capnography (ETCO2) is commonly implemented by emergency medical services professionals in resuscitation and can serve as an ideal biomarker for resuscitation. However, there are no effective conceptual frameworks utilizing continuous ETCO2 data. In this manuscript, we detail a conceptual framework using AI and machine learning techniques to leverage ETCO2 in guided resuscitation.

Keywords: Artificial intelligence, cardiac arrest, resuscitation, end tidal capnography, reinforcement learning

1. Introduction

Half a million Americans suffer from out-of-hospital cardiac arrest (OHCA) annually, with only $7-10\%$ surviving to hospital discharge.[7;5;3] Cardiac arrest is a dynamic process[31;20]; where the effectiveness of interventions varies as time elapses and cardiac physiology evolves. Current resuscitation algorithms rigidly dictate defined interventions at fixed time intervals regardless of individual patient characteristics or evolving cardiac pathophysiology. Customizing resuscitation interventions based on the dynamic state of the arrested heart and the individual characteristics of the patients with EMS interventions has the strongest potential to improve outcomes.

2. Defining End Tidal Capnography

Real-time, quantitative feedback or biomarkers are needed to guide intra-arrest efforts toward clear benchmarks during resuscitation. End-tidal carbon dioxide (ETCO2) fits the profile of an ideal continuous biomarker for guiding resuscitation as it is the tecnique of continuously measuring carbon dioxide exhaled from the lungs. ETCO@ is widely recognized, easy to use, and is commonly implemented by emergency medical services (EMS) professionals in resuscitation.[25] End-tidal carbon dioxide (ETCO2) has been historically reserved for confirming endotracheal tube placement during resuscitation and monitoring a patient's respiratory status[22;24]. Correlative studies have shown large variability in measured blood gas PaCO2 and ETCO2; [26] thus, it is important to clarify that ETCO2 capnography is not just a representation of blood gas CO2. It is a dynamic real-time monitor of the multiple pathophysiologic derangements during cardiac arrest. ETCO2 capnography is dependent on three

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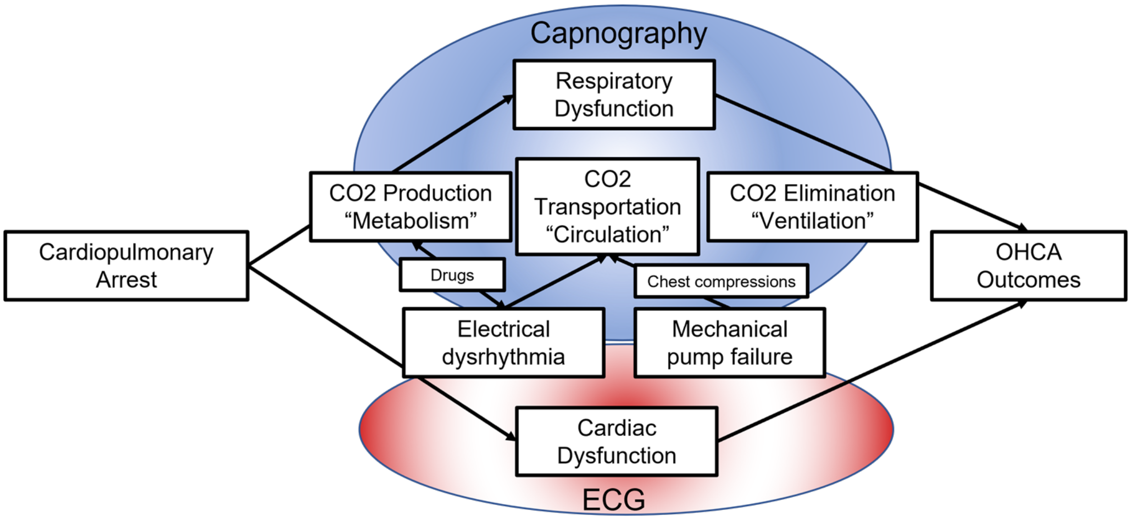

Figure 1. Pathophysiology underlying ETCO2 capnography during OHCA resuscitation. Capnography (blue) reflects multiple changes that occur during resuscitation. ECG (red) reflects changes in cardiac electrical rhythm.

main pathways: (1) CO2 Production or "Metabolism", (2) CO2 Transportation to Alveoli for Exchange or "Circulation", and (3) CO2 elimination through alveolar diffusion or "Ventilation". Cardiopulmonary arrest dysregulates all three pathways altering ETCO2 values and capnography waveforms as described in Figure 1. Cardiac arrhythmias, mechanical failure, etiology of arrest, resuscitation drugs, and chest compression efforts all impact ETCO2[15;29;28;13;12].

3. ETCO2 in Cardiac Arrest and Barriers to Analysis

Complex dynamic ETCO2 features must be fully defined in order to leverage ETCO2 in guided resuscitation. During cardiac arrest ETCO2 values are typically low; this is because in the immediate aftermath of the heart stopping, there is very little blood flow to circulate carbon dioxide from the body to the lungs. Even CPR chest compressions do not result in circulation equivalent to normal physiologic cardiac output, which results in decreased CO2 delivery to the lungs. [19] CO2 production continues throughout the body through aerobic metabolism. With the establishment of circulation, return of spontaneous circulation (ROSC), and corresponding dramatic improvements in cardiac output, we and others have shown ETCO2 dramatically increases and produces an ETCO2 spike.[10;18;6] With continued ventilation, CO2 is eliminated, and ETCO2 values approach a new steady-state-level. Despite continuous ETCO2 availability recordings for decades, its full potential for use in resuscitation was previously not attainable. Prior studies used crude, discrete, and random time point ETCO2 measures to correlate with ROSC[23;9;16;27]. These measurements were likely simplistically performed due to the sheer volume of waveforms that are available for analysis in continuous ETCO2 capnography recordings during resuscitation. This resulted in disagreement on the discrete level of ETCO2 that predicts return of circulation, and reported ROSC detection as low as $20 - 33\%$.[18] The most comprehensive data analysis was compiled by an International Liaison Committee On Resuscitation systematic review that stated continuous ETCO2 capnography through trending ETCO2 may be a better predictor of cardiac arrest outcomes.[23;9;4;14] However, continuous dimensions of ETCO2 capnography -such as the temporal trends - have yet to be fully characterized in resuscitation.[23;10;21],Manual CPR interpretation is time intensive; thus, use of automated signal processing techniques of continuous chest compression and ETCO2 capnography are needed to analyze continuous CPR process data files. Through automated signal processing, vital ETCO2 information such as ETCO2 value change, rate of change, chest compression, and ventilation qualities can quickly be assessed. Further connecting temporal trends in ETCO2 with time-sensitive interventions such as medications during resuscitation thus far has been too complex for linear regression models.

4. Preliminary Model Building: Defining ETCO2 real-time values in relation to Cardiac Arrest State

The use of machine learning to differentiate resuscitation interventions, patient specific characteristics, and ETCO2 capnography patterns will free us from the constraints of conventional statistical approaches, while allowing a novel approach to resuscitation in an equitable dynamic way. There are plausible physiologic connections between ETCO2 capnography, resuscitation interventions, and OHCA outcomes.In this conceptual paper we detail the framework for modeling continuous ETCO2 in guided resuscitation.

As an initial step, we applied previously validated signal processing techniques[10] to analyze ETCO2 waveforms to first determine if there was a trend in ETCO2 in patients who achieved ROSC in comparison to those who did not achieve ROSC as shown in Figure 2. We observed a significant upward trend in ETCO2 in ROSC patients that does not occur in non-ROSC patients ($p < 0.01$). This emphasizes the deeper analysis of ETCO2 required to causally define ETCO2 trends in relation to patient demographics, resuscitation interventions and outcomes.

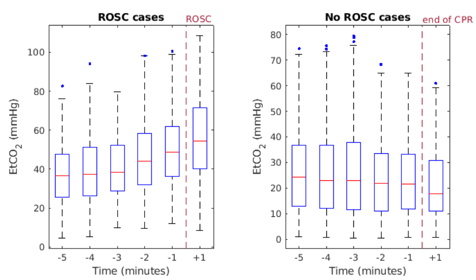

Figure 2. Preliminary Analysis of 1000 cases in PART trial. ROSC cases have a positive trend of ETCO2 that begins several minutes before ROSC (red dashed line). No ROSC cases have a static ETCO2 that remains until end of CPR.

The use of advanced machine learning (ML) techniques to characterize ETCO2 capnography variability may offer key insights into the dynamics of ETCO2 in resuscitation. We propose to model the dynamics of cardiac states during resuscitation as a directed probabilistic graphical model as shown in figure 3. Motivated by the previously suggested Markovian model for the evolution of the cardiac state during resuscitation,[30] we will jointly model EMS actions, physiological measurements, and ventilation quality metrics for the underlying cardiac states described in Table 1.[17] The causal relationship between

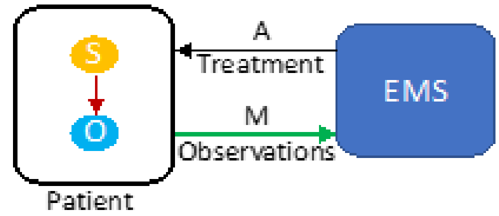

Figure 3. Dynamic model representing the evolution of cardiac state S in CPR process with treatments A and indirectly observed through measurements M.

the treatment option denoted by A, quality metrics denoted by M, and the underlying cardiac state denoted by S is captured by the joint probability distribution dictated by the edges of the graph. Specifically, the action set A will be enumerated by a finite discrete set of options such as intubation time, epinephrine time, or quality metrics like chest compression depth. The measurements consist of the ETCO2 capnograph, blood pressure, and ECG. The underlying state space comprises the clinically labeled cardiac health states such as ROSC. We hypothesize that the transition between states is a semi-Markov process where the time taken in a particular state is also stochastic and is a function of the current state.[1] “Hidden” or unrecognized patterns may emerge; for example, the shape of the ETCO2 capnography waveform may provide pertinent information. The probabilistic model can be either constructed using parametric methods or by composing the dependence and causal structure in the deep learning framework. We will utilize deep learning algorithms to identify these hidden patterns and estimate the probability distribution by composing the graphical model from the features learned by neural networks.[2] The deep learning architecture with attention mechanism will help with the delineation of the capnogram of each ventilation. We will use ML methods to characterize the dynamic relation between resuscitation actions—as quantified by chest compression quality metrics—and ETC02 capnograhy variables. We will define chest compression quality metrics as quantitative measures of Actions and ETCO2 capnography changes as Observation

5. Developing reward-based algorithm guided by ETCO2

The model proposed in Figure 4 can be used as a framework for predicting the trajectory of evolution of cardiac state for a given set of treatment options. We will define 1) ML models and 2) deep learning models to predict outcome (ROSC, survival, re-arrest

Table 1. Parameters to model the evolution of the Cardiac states during OHCA.

Observations	EMS interventions	Cardiac states
Raw ETCO2 Value Change in ETCO2 ETCO2 Plateau duration and waveform shape Ventilation Rate Thoracic Impedance Amplitude and Duration Blood Pressure ECG	Advanced Airway placement Chest Compressions (Rate, Depth) Medicines (Epinephrine, Sodium Bicarbonate, Amiodarone) Defibrillation Mechanical CPR	Asystole Ventricular Tachycardia/ Ventricular Fibrillation PEA Pseudo-PEA Transient ROSC Sustained ROSC

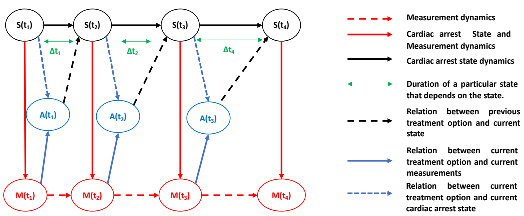

Figure 4. Probabilistic Graphical model representing the underlying state S that comprises the cardiac state during resuscitation with treatments A performed by EMS and incorporating continuous indirect physiological measurements M. The model includes the time the patient spends in each state as part of the stochastic model.

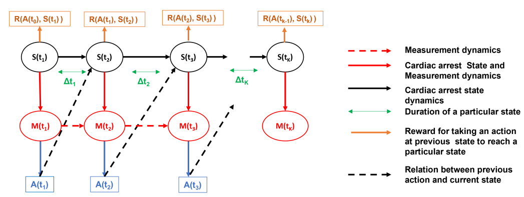

Figure 5. Partially observable semi-Markov decision process representing Dynamic Treatment algorithm for guiding resuscitation strategy. The reward function maps the current cardiac state and the treatment options. The objective is to choose feasible treatment strategies that lead to favorable outcomes indicated by accumulated rewards over the treatment epoch.

and death). In (1) models, the mean values of the ETCO2 characteristics will be used alongside support vector machines, random forests, and other regressive binary classifiers. The model should show the combination of features associated with positive and negative outcomes. Additionally, patient-specific clinical information (type of airway device, initial rhythm, bystander CPR, age, or other classic Utstein criteria) can be included. In (2), the time evolution of the ETCO2 features and the sequence of actions will be directly fed into our model, and the likelihood of the termination state will be determined. The maximum likelihood estimator will be used to classify the termination state or health outcome of the CPR process. We will evaluate the classification accuracy of the models using receiver operative characteristic curve measures such as sensitivity, specificity, accuracy, and area-under-the-curve. Cross validation techniques will be used to train and validate the predictive models. Finally, we propose a reinforcement-based learning strategy for finding the treatment procedure that guarantees favorable survival outcomes[32]. The dynamics of cardiac health is paired with factors estimated to design reward functions that promote equitable and positive outcomes. We will extend the neural network structure utilized in Figure 5 to incorporate reward structures to estimate the sequence of optimal treatment options[8;11]

6. Conclusions

AI has advanced healthcare by relating previously complex conditions with novel treatment modalities that promote favorable outcomes. Leveraging ML methods to define the complex relationship of ETCO2 in resuscitation can lead to personalized resuscitation. ETCO2 guided resuscitation that is responsive to fluctuating cardiac pathophysiology has the most promise in improving outcomes from OHCA.

References

[1] Alaa, A. M., Hu, S., and Schaar, M. (2017). Learning from clinical judgments: Semi-markov-modulated marked hawkes processes for risk prognosis. In *International Conference on Machine Learning*, pages 60–69. PMLR.

[2] Alaa, A. M. and van der Schaar, M. (2019). Attentive state-space modeling of disease progression. *Advances in neural information processing systems*, 32.

[3] Benjamin, E. J., Muntner, P., Alonso, A., Bittencourt, M. S., Callaway, C. W., Carson, A. P., Chamberlain, A. M., Chang, A. R., Cheng, S., Das, S. R., et al. (2019). Heart disease and stroke statistics—2019 update: a report from the american heart association. *Circulation*, 139(10):e56–e528.

[4] Brinkrolf, P., Borowski, M., Metelmann, C., Lukas, R.-P., Pidde-Küllenberg, L., and Bohn, A. (2018). Predicting rosc in out-of-hospital cardiac arrest using expiratory carbon dioxide concentration: Is trend-detection instead of absolute threshold values the key? *Resuscitation*, 122:19–24.

[5] Chan, P. S., McNally, B., Tang, F., and Kellermann, A. (2014). Recent trends in survival from out-of-hospital cardiac arrest in the united states. *Circulation*, 130(21):1876–1882.

[6] Crickmer, M., Drennan, I. R., Turner, L., and Cheskes, S. (2021). The association between end-tidal co2 and return of spontaneous circulation after out-of-hospital cardiac arrest with pulseless electrical activity. *Resuscitation*, 167:76–81.

[7] Daya, M. R., Schmicker, R. H., Zive, D. M., Rea, T. D., Nichol, G., Buick, J. E., Brooks, S., Christenson, J., MacPhee, R., Craig, A., et al. (2015). Out-of-hospital cardiac arrest survival improving over time: results from the resuscitation outcomes consortium (roc). *Resuscitation*, 91:108–115.

[8] Du, J., Futoma, J., and Doshi-Velez, F. (2020). Model-based reinforcement learning for semi-markov decision processes with neural odes. *Advances in Neural Information Processing Systems*, 33:19805–19816.

[9] Eckstein, M., Hatch, L., Malleck, J., McClung, C., and Henderson, S. O. (2011). End-tidal co2 as a predictor of survival in out-of-hospital cardiac arrest. *Prehospital and disaster medicine*, 26(3):148–150.

[10] Elola, A., Aramendi, E., Irusta, U., Alonso, E., Lu, Y., Chang, M. P., Owens, P., and Idris, A. H. (2019). Capnography: A support tool for the detection of return of spontaneous circulation in out-of-hospital cardiac arrest. *Resuscitation*, 142:153–161.

[11] Fatemi, M., Wu, M., Petch, J., Nelson, W., Connolly, S. J., Benz, A., Carnicelli, A., and Ghassemi, M. (2022). Semi-markov offline reinforcement learning for healthcare. In *Conference on Health, Inference, and Learning*, pages 119–137. PMLR.

[12] Gazmuri, R. J. and Kube, E. (2003). Capnography during cardiac resuscitation: a clue on mechanisms and a guide to interventions. *Critical Care*, 7:1–3.

[13] Grmec, S. and Mally, S. (2006). Vasopressin improves outcome in out-of-hospital cardiopulmonary resuscitation of ventricular fibrillation and pulseless ventricular tachycardia: a observational cohort study. *Critical Care*, 10:1–7.

[14] Gutiérrez, J. J., Leturiondo, M., Ruiz de Gauna, S., Ruiz, J. M., Azcarate, I., González-Otero, D. M., Urtusagasti, J. F., Russell, J. K., and Daya, M. R. (2021). Assessment of the evolution of end-tidal carbon dioxide within chest compression pauses to detect restoration of spontaneous circulation. *Plos one*, 16(5):e0251511.

[15] Kolar, M., Križmarić, M., Klemen, P., and Grmec, Š. (2008a). Partial pressure of end-tidal carbon dioxide successful predicts cardiopulmonary resuscitation in the field: a prospective observational study. *Critical care*, 12:1–13.

[16] Kolar, M., Križmarić, M., Klemen, P., and Grmec, Š. (2008b). Partial pressure of end-tidal carbon dioxide successful predicts cardiopulmonary resuscitation in the field: a prospective observational study. *Critical care*, 12:1–13.

[17] Koller, D. and Friedman, N. (2009). *Probabilistic graphical models: principles and techniques*. MIT press.

[18] Lui, C. T., Poon, K. M., and Tsui, K. L. (2016). Abrupt rise of end tidal carbon dioxide level was a specific but non-sensitive marker of return of spontaneous circulation in patient with out-of-hospital cardiac arrest. *Resuscitation*, 104:53–58.

[19] Lurie, K. G., Nemergut, E. C., Yannopoulos, D., and Sweeney, M. (2016). The physiology of cardiopulmonary resuscitation. *Anesthesia & Analgesia*, 122(3):767–783.

[20] Marquez, A. M., Morgan, R. W., Ross, C. E., Berg, R. A., and Sutton, R. M. (2018). Physiology-directed cardiopulmonary resuscitation: advances in precision

monitoring during cardiac arrest. *Current opinion in critical care*, 24(3):143–150.

[21] Merchant, R. M., Topjian, A. A., Panchal, A. R., Cheng, A., Aziz, K., Berg, K. M., Lavonas, E. J., and Magid, D. J. (2020). Part 1: executive summary: 2020 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, 142(16 Suppl 2):S337–S357.

[22] Ornato, J. P., Shipley, J. B., Racht, E. M., Slovis, C. M., Wrenn, K. D., Pepe, P. E., Almeida, S.-L., Ginger, V. F., and Fotre, T. V. (1992). Multicenter study of a portable, hand-size, colorimetric end-tidal carbon dioxide detection device. *Annals of emergency medicine*, 21(5):518–523.

[23] Paiva, E. F., Paxton, J. H., and O'Neil, B. J. (2018). The use of end-tidal carbon dioxide (etco2) measurement to guide management of cardiac arrest: a systematic review. *Resuscitation*, 123:1–7.

[24] Panchal, A. R., Bartos, J. A., Cabañas, J. G., Donnino, M. W., Drennan, I. R., Hirsch, K. G., Kudenchuk, P. J., Kurz, M. C., Lavonas, E. J., Morley, P. T., et al. (2020). Part 3: adult basic and advanced life support: 2020 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation*, 142(16_Suppl_2):S366–S468.

[25] Panchal, A. R., Rivard, M. K., Cash, R. E., Corley Jr, J. P., Jean-Baptiste, M., Chrzan, K., and Gugiu, M. R. (2022). Methods and implementation of the 2019 ems practice analysis. *Prehospital Emergency Care*, 26(2):212–222.

[26] Prause, G., Hetz, H., Lauda, P., Pojer, H., Smolle-Juettner, F., and Smolle, J. (1997). A comparison of the end-tidal-co2 documented by capnometry and the arterial pco2 in emergency patients. *Resuscitation*, 35(2):145–148.

[27] Rognås, L., Hansen, T. M., Kirkegaard, H., and Tønnesen, E. (2014). Predicting the lack of rosc during pre-hospital cpr: Should an end-tidal co2 of 1.3 kpa be used as a cut-off value? *Resuscitation*, 85(3):332–335.

[28] Sheak, K. R., Wiebe, D. J., Leary, M., Babaeizadeh, S., Yuen, T. C., Zive, D., Owens, P. C., Edelson, D. P., Daya, M. R., Idris, A. H., et al. (2015). Quantitative relationship between end-tidal carbon dioxide and cpr quality during both in-hospital and out-of-hospital cardiac arrest. *Resuscitation*, 89:149–154.

[29] Shibutani, K., Muraoka, M., Shirasaki, S., Kubal, K., Sanchala, V. T., and Gupte, P. (1994). Do changes in end-tidal pco2 quantitatively reflect changes in cardiac output? *Anesthesia & Analgesia*, 79(5):829–833.

[30] Skogvoll, E., Eftestøl, T., Gundersen, K., Kvaløy, J. T., Kramer-Johansen, J., Olasveengen, T. M., and Steen, P. A. (2008). Dynamics and state transitions during resuscitation in out-of-hospital cardiac arrest. *Resuscitation*, 78(1):30–37.

[31] Weisfeldt, M. L. and Becker, L. B. (2002). Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *Jama*, 288(23):3035–3038.

[32] Zhang, J. and Bareinboim, E. (2019). Near-optimal reinforcement learning in dynamic treatment regimes. *Advances in Neural Information Processing Systems*, 32.