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Clinical paper

Value of capnography to predict defibrillation success in out-of-hospital cardiac arrest

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Abstract

Background and aim: Unsuccessful defibrillation shocks adversely affect survival from out-of-hospital cardiac arrest (OHCA). Ventricular fibrillation (VF) waveform analysis is the tool-of-choice for the non-invasive prediction of shock success, but surrogate markers of perfusion like end-tidal CO_2 ($EtCO_2$) could improve the prediction. The aim of this study was to evaluate $EtCO_2$ as predictor of shock success, both individually and in combination with VF-waveform analysis.

Materials and methods: In total 514 shocks from 214 OHCA patients (75 first shocks) were analysed. For each shock three predictors of defibrillation success were automatically calculated from the device files: two VF-waveform features, amplitude spectrum area (AMSA) and fuzzy entropy (FuzzyEn), and the median $EtCO_2$ ($MEtCO_2$) in the minute before the shock. Sensitivity, specificity, receiver operating characteristic (ROC) curves and area under the curve (AUC) were calculated, for each predictor individually and for the combination of $MEtCO_2$ and VF-waveform predictors. Separate analyses were done for first shocks and all shocks.

Results: $MEtCO_2$ in first shocks was significantly higher for successful than for unsuccessful shocks (31 mmHg/25 mmHg, $p < 0.05$), but differences were not significant for all shocks (32 mmHg/29 mmHg, $p > 0.05$). $MEtCO_2$ predicted shock success with an AUC of 0.66 for first shocks, but was not a predictor for all shocks (AUC 0.54). AMSA and FuzzyEn presented AUCs of 0.76 and 0.77 for first shocks, and 0.75 and 0.75 for all shocks. For first shocks, adding $MEtCO_2$ improved the AUC of AMSA and FuzzyEn to 0.79 and 0.83, respectively.

Conclusions: $MEtCO_2$ predicted defibrillation success only for first shocks. Adding $MEtCO_2$ to VF-waveform analysis in first shocks improved prediction of shock success. VF-waveform features and $MEtCO_2$ were automatically calculated from the device files, so these methods could be introduced in current defibrillators adding only new software.

Keywords: Ventricular fibrillation, Shock outcome prediction, End-tidal CO_2 ($EtCO_2$), Out-of-hospital cardiac arrest, Amplitude spectrum area (AMSA), Fuzzy entropy

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Introduction

Cardiopulmonary resuscitation (CPR) and electrical defibrillation are the cornerstones of therapy for out-of-hospital cardiac arrest (OHCA). Defibrillation shocks are the only effective way to terminate ventricular fibrillation (VF) and restore a perfusing rhythm. However, the mechanisms of defibrillation are not fully understood,[1] and many electrical shocks are unsuccessful. Unsuccessful shocks may cause myocardial damage,[2] and interruptions in chest compressions to deliver the shock are associated with a rapid decrease in coronary perfusion pressure.[3] All these factors adversely affect survival, and compromise the success of later shocks in prolonged cardiac arrest.[2–4]

VF waveform analysis has been extensively studied as a non-invasive tool to predict shock success, and thus optimize CPR/defibrillation therapy.[5] Many VF waveform features have been proposed for this purpose,[6–9] ranging from classical amplitude, slope or spectral analyses of VF,[6,10] to quantitative measures of its non-linear nature such as Poincare plot[11] and detrended fluctuation analyses,[12] fractal dimension[13] or Hurst and Scaling exponents.[13,14] The best known VF-waveform feature is amplitude spectrum area (AMSA), a measure of amplitude and frequency distribution of VF.[15,16] Recently, VF waveform regularity and predictability measures based on entropy estimates have been shown to accurately predict shock success,[17,18] and fuzzy entropy (FuzzyEn) was identified as the most accurate predictor based on entropy estimates outperforming other classical predictors.[17]

Advanced life support guidelines recommend continuous use of end-tidal carbon dioxide ($EtCO_2$) to monitor quality of CPR, confirm endotracheal intubation, detect return of spontaneous circulation and guide the rescuer during CPR.[19] $EtCO_2$, measured as the peak value of the capnogram at the end of exhalation, is a surrogate indicator of coronary perfusion during CPR.[20] Abrupt increments of $EtCO_2$ and higher values of $EtCO_2$ have been associated with restoration of spontaneous circulation, quality of CPR and patient outcome.[21–26] Higher $EtCO_2$ has been linked to shock success in animal models,[20] and positive correlations between AMSA and $EtCO_2$ have been found in animal data[27] and during a prolonged case of refractory VF in OHCA.[28] Although the evidence is not conclusive, the mean $EtCO_2$ in the minute preceding defibrillation is associated to defibrillation success,[29] and the accuracy of defibrillation success prediction may be increased by combining $EtCO_2$ and VF-waveform features.[30]

The aim of this study was to evaluate the value of capnography for the prediction of defibrillation success using OHCA data, and to develop automatic prediction methods based on the capnogram. For that purpose the median $EtCO_2$ ($MEtCO_2$) in the minute before the shock was used. The assessment was done in two ways, using $MEtCO_2$ alone, and combining $MEtCO_2$ with AMSA and FuzzyEn to evaluate its aggregate value for the prediction of shock success.

Materials and methods

Data materials

The study dataset was obtained from OHCA patients treated by the DFW Center for Resuscitation Research (UTSW, Dallas, TX) and the Tualatin Valley Fire and Rescue (Portland, OR) between 2010 and 2016. Data collected using the MRx monitor-defibrillator (Philips Medical Systems, Andover, MA, USA) was analysed. MRx data included the ECG, compression depth from a CPR-assist pad, and the capnogram acquired using Microstream technology (sidestream acquisition). The ECG was recorded with a 0–50 Hz bandwith, 250 Hz sampling rate and a resolution of 1.03 μV per least significant bit. The capnogram was acquired with a sampling rate of 40/125 Hz and a resolution of 0.004 mmHg per bit. Cases were included in the study if the patient presented VF cardiac arrest, and had at least one defibrillation attempt with: concurrent recordings of capnogram (to compute $MEtCO_2$) and compression depth (to assess CPR quality) in the 1-min interval before the shock, an artifact free ECG in the 5-s interval before the shock to compute the VF-waveform features, and 1-min post shock ECG to annotate whether the shock was successful.

All shocks were visually reviewed and annotated by two experienced biomedical engineers (EA, UI). Shock success was defined as the appearance of sustained QRS complexes with a rate above 40 beats/min within 60-s after the shock.[16] The appearance of sustained QRS complexes after the shock has been a widely accepted criterion for the definition of shock success in many previous studies.[8,29–33] Fig. 1 shows two representative examples. In the example above the patient presents a rhythm with sustained QRS complexes (rate around 60 beats/min) after the shock, the bottom example shows a case with refractory VF. In both shocks there was a minute of end-tidal CO_2 data before the shock to compute $MEtCO_2$.

Predictors of defibrillation success

Three predictors of defibrillation success were computed, $MEtCO_2$ and two established VF waveform predictors, AMSA and FuzzyEn. $MEtCO_2$ was calculated using a 1-minute interval before the shock. First, ventilations were automatically detected in the capnogram using the algorithm proposed in Ref.[34], which is very accurate even in the presence of chest compressions. Then, the $EtCO_2$ value for each ventilation was obtained as the maximum value of the CO_2 waveform during the alveolar plateau (see Fig. 1). $MEtCO_2$ was the median value of the $EtCO_2$ values. VF waveform features were computed using a 2-s interval before the shock, leaving a 1-s guard interval to avoid interferences (see Fig. 1). The ECG was bandpass filtered (0.5–30 Hz) using forward-backward filtering and an order 8 elliptic filter to remove baseline oscillations and high frequency noise. The spectral amplitudes of the ECG were computed using the Fast Fourier Transform, and AMSA was obtained in the 2–48 Hz frequency range as $\mathrm{AMSA} = \sum A_k f_k$, where A_k is the amplitude corresponding to frequency f_k.[16] FuzzyEn quantifies the regularity of VF by analyzing repetitive patterns along the waveform. VF-amplitude was considered in the calculation of FuzzyEn as proposed in Refs.[17,18], because VF-amplitude has been shown to correlate to the state of the myocardium.[35]

Statistical analysis

CPR quality metrics associated with every shock were computed using the 1-min interval before the shock. The mean chest compression rate (CR) and depth (CD), were obtained using the compression depth signal from the CPR assist pad, the mean ventilation rate (VR) was obtained from the ventilations detected in the capnogram. CPR quality metrics, $MEtCO_2$, AMSA and FuzzyEn are reported as median (interquartile range, IQR) for successful and unsuccessful shocks because their distributions did not pass the Anderson-Darling normality test. Distributions for successful and

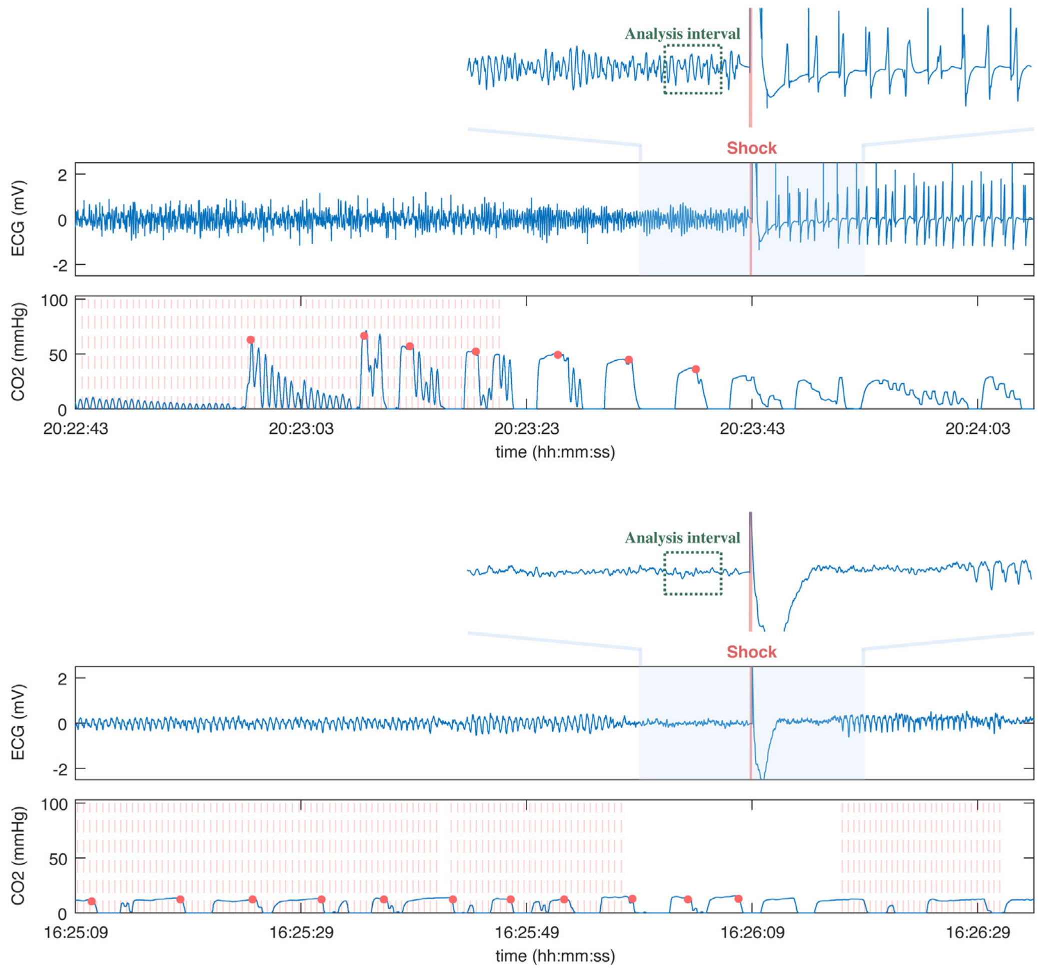

Fig. 1 – Representative examples of two shocks, a successful shock (top) and an unsuccessful shock with refractory VF (below). VF-waveform features (AMSA and FuzzyEn) were computed in the 2-s analysis interval with a 1-s guard before the shock. MEtCO$_2$ and the CPR metrics were computed in the 1-min interval before the shock. Chest compressions obtained from the compression depth are marked as vertical red lines, and the EtCO$_2$ values for each ventilation as red dots.

unsuccessful shocks were compared using the Mann–Whitney *U*-test, and differences were considered statistically significant for $p<0.05$.

Univariate logistic regression analyses were done for all predictors and CPR quality metrics. The parameters that showed significant differences ($p<0.05$) were further included in multivariate logistic regression models. The analyses were done separately for first shocks and all shocks. Data was randomly partitioned patient-wise into training (60%) to fit the models, and test (40%) to report the results. The process was repeated 100 times to obtain the statistical distribution of the performance metrics. For patients with multiple shocks (all shocks group) generalized estimating equations with time adjusted correlations were used to account for repeated measures.[36] The performance of the models was evaluated in terms of sensitivity (Se), the capacity to identify successful shocks, and specificity (Sp), the capacity to identify unsuccessful shocks. ROC curves were obtained and the area under the curve (AUC) was used to compare the accuracy of the models.[37] The optimal point in the ROC curve was determined using the Youden index, which gives equal importance to Se and Sp.[38] All calculations were done using the Statistics and Machine Learning toolbox from MATLAB (Mathworks Inc., Natick, MA, USA).

Results

A total of 1933 cases from the study period were analyzed and 214 met the inclusion criteria. In the study dataset the mean (SD) duration of the cases was 41 (15) min, 77% of patients were male, and the median (IQR) age was 60 (51–71) years. A total of 76 patients achieved ROSC, and 12% survived. There were 514 shocks that met the inclusion criteria, 196 were successful and 318 were not. The median number of shocks included per patient was 2 (1–3). In 75 cases first shocks were available, 33 of which were successful.

Table 1 compares the distributions of the CPR quality variables for successful and unsuccessful shocks, and the *p*-value of an univariate analysis for each individual variable. There were no significant differences in CR and VR, although CD was significantly larger for unsuccessful shocks (4.7 cm vs 4.9 cm). Similar values were observed for the subgroup of first shocks. The univariate analyses for the CPR quality metrics confirmed these results, with *p*-values for the models based on CR and VR not significant for both all shocks and first shocks groups, and significant for CD in both groups.

Table 1 – Distributions of the CPR quality parameters for all shocks and for the first shocks. The abbreviations are: VR, ventilation rate; CR, compression rate; CD, compression depth.

	All shocks			First shocks		
	Success	No Success	*p*	Success	No Success	*p*
VR (min^{-1})	10.0 (7.0–12.0)	9.0 (7.0–12.0)	>0.05	9.0 (5.7–10)	8.0 (6.0–9.0)	>0.05
CR (min^{-1})	107 (100–115)	107 (100–115)	>0.05	109 (100–115)	107 (100–114)	>0.05
CD (cm)	4.7 (4.1–5.2)	4.9 (4.3–5.4)	<0.05	4.4 (3.9–5.0)	5.0 (4.4–5.4)	<0.05

Fig. 2 compares the distributions (boxplots) of the shock success predictors for successful and unsuccessful shocks, both for all shocks (top) and first shocks (bottom). VF-waveform features were significantly different between successful and unsuccessful shocks in all cases. $METCO_2$ was larger for successful shocks in both cases, but the difference between successful and unsuccessful shocks was only statistically significant for the subgroup of first shocks. For this subgroup the median $METCO_2$ value was 31.0 (22.5–50.3) mmHg for successful shocks and 25.0 (11.3–34.5) mmHg for unsuccessful shocks. Fig. 3 shows the proportion (raw percentages) of successful and unsuccessful first shocks for three ranges of $METCO_2$. $METCO_2$ under 20 mmHg are associated to low quality CPR,[39,40] and values above 40 mmHg to ROSC.[40] We observed a large increase in the proportion of successful shocks from 25% for $METCO_2 < 20$ mmHg to over 60% for $METCO_2 > 40$ mmHg.

Table 2 summarizes the results of the univariate and multivariate analyses with the test set for all shocks and first shocks. VF waveform features, AMSA and FuzzyEn, were significant ($p < 0.05$) for first

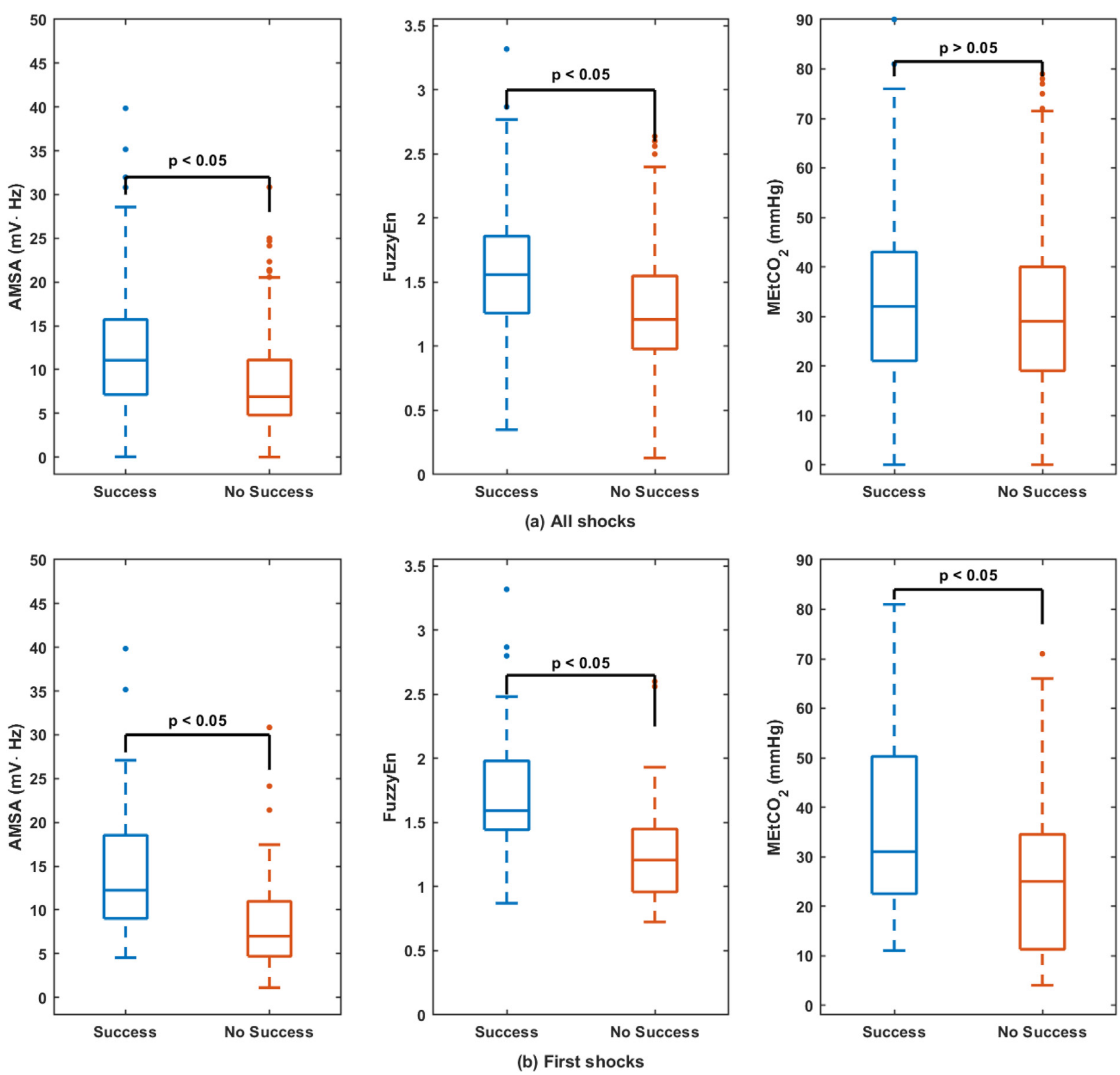

Fig. 2 – Boxplots of the defibrillation success predictors, for all shocks (top) and for the first shocks (bottom).

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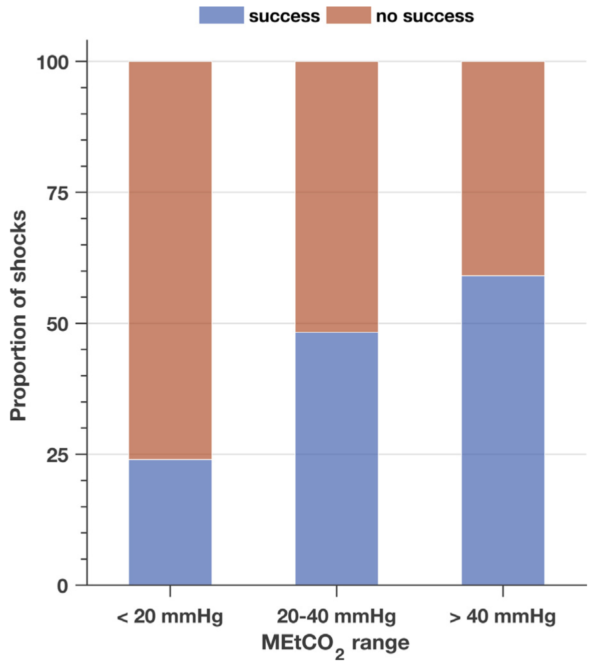

Fig. 3 – Distribution of first shocks as successful or not successful for three representative intervals of $MEtCO_2$.

shocks and all shocks. AMSA was not significant in multivariate models that combined AMSA and FuzzyEn, so AMSA and FuzzyEn were considered separately in multivariate analyses (Table 2). For all shocks CD was significant, but $MEtCO_2$ was not and it was not considered for multivariate analyses. Adding CD to AMSA or FuzzyEn increased the AUC by less than 1-point. For first shocks both $MEtCO_2$ and CD were significant, but $MEtCO_2$ contributed more than CD to multivariate models. The AUC of AMSA/FuzzyEn increased by 3/6 points when $MEtCO_2$ was added, but adding CD only increased the AUC of AMSA by 3 points, showing no improvement for FuzzyEn. For AMSA, $MEtCO_2$ and CD contributed independently but did not outperform the model with FuzzyEn and $MEtCO_2$ which had the largest AUC for first shocks. Fig. 4 shows how VF-waveform features and $MEtCO_2$ values are distributed, and how first successful shocks concentrate on high values of the VF-waveform predictors and $MEtCO_2$ (north-east corner). For first shocks $MEtCO_2$ contributes to the separability of successful and unsuccessful shocks.

Discussion

This study provides new evidence on value of $MEtCO_2$ for the prediction of defibrillation success. $MEtCO_2$ showed predictive power only for first shock attempts, for which it also added predictive power to VF-waveform features. Furthermore, all $MEtCO_2$ calculations and VF-feature calculations were performed automatically using the waveforms recorded by the monitor defibrillator, and could therefore be integrated into current equipment adding only new software.

Many studies have analysed the value of $EtCO_2$ in cardiac arrest as a surrogate marker of perfusion, with emphasis on its value to monitor CPR quality[21,22] or to provide an early indication of return of spontaneous circulation.[23–25,41] However, little is known on its value to predict defibrillation success. In our data, low $MEtCO_2$ values in the first shock were associated to unsuccessful shocks, and higher $MEtCO_2$ values were an indication of an increased probability of successful shocks (Fig 3). First shocks with $MEtCO_2$ values under 11 mmHg (n=10) were always unsuccessful, while 60% were successful for $MEtCO_2$ above 40 mmHg (n=22). Our low $MEtCO_2$ cutoff for unsuccessful shocks is similar to the values observed by Savastano et al.,[29] and confirm an $MEtCO_2$ value around 10 mmHg may be used as an indication to delay the shock. These findings are aligned with the European[19] and American[40] guidelines which suggest 10 mmHg as an indicator of good quality CPR. However, our cutoffs for successful shocks were higher than the 31 mmHg proposed by Savastano et al. This suggests that differences in the measurements of $EtCO_2$ might be

Table 2 – ROC curve analysis for the four individual predictors and for the combination of VF-waveform predictors, $MEtCO_2$ and CD when each one alone is significant. All features were significant with a $p<0.05$, except $MEtCO_2$ for all shocks (*), so $MEtCO_2$ combinations for all shocks are not reported. The median (IQR) of the distributions are reported for the AUC, Se and Sp with the test set, after repeating training/test partitioning 100 times. The Se/Sp are given for the optimal point (Youden index).

	Data base					
	All shocks			First shocks		
	AUC	Se (%)	Sp (%)	AUC	Se (%)	Sp (%)
Univariate						
AMSA	0.75 (0.72–0.75)	79.8 (71.4–85.5)	63.2 (58.5–71.6)	0.76 (0.72–0.82)	82.1 (76.2–88.4)	59.9 (52.9–64.7)
FuzzyEn	0.75 (0.73–0.77)	73.6 (67.1–78.8)	69.4 (64.1–75.6)	0.77 (0.73–,0.82)	83.0 (78.1–89.5)	62.5 (58.8–70.6)
$MEtCO_2$	0.54 (0.51–0.57)*	48.1 (42.0–69.3)	66.1 (43.3–72.1)	0.66 (0.60–0.71)	69.1 (57.9–86.5)	53.0 (38.3–64.7)
CD	0.58 (0.56–0.60)	56.2 (34.6–75.7)	62.7 (42.2–82.8)	0.65 (0.61–0.72)	76.9 (53.8–92.3)	58.8 (35.3–85.3)
Multivariate						
AMSA+CD	0.75 (0.73–0.77)	78.5 (72.1–84.3)	63.7 (59.2–70.3)	0.76 (0.72–0.81)	69.2 (61.5–84.6)	82.4 (70.6–88.2)
AMSA+$MEtCO_2$	–	–	–	0.79 (0.75–0.85)	85.1 (81.2–89.8)	60.7 (52.9–67.6)
AMSA+$MEtCO_2$+CD	–	–	–	0.82 (0.77–0.86)	92.3 (84.6–96.2)	70.6 (64.7–82.4)
FuzzyEn+CD	0.76 (0.73–0.78)	79.5 (75.8–82.2)	65.1 (60.6–69.2)	0.80 (0.74–0.85)	84.6 (76.9–92.3)	76.5 (70.6–82.4)
FuzzyEn+$MEtCO_2$	–	–	–	0.83 (0.78–0.88)	85.9 (80.5–91.6)	65.4 (58.8–70.6)
FuzzyEn+$MEtCO_2$+CD	–	–	–	0.83 (0.78–0.88)	84.6 (76.9–92.3)	82.4 (70.6–88.2)

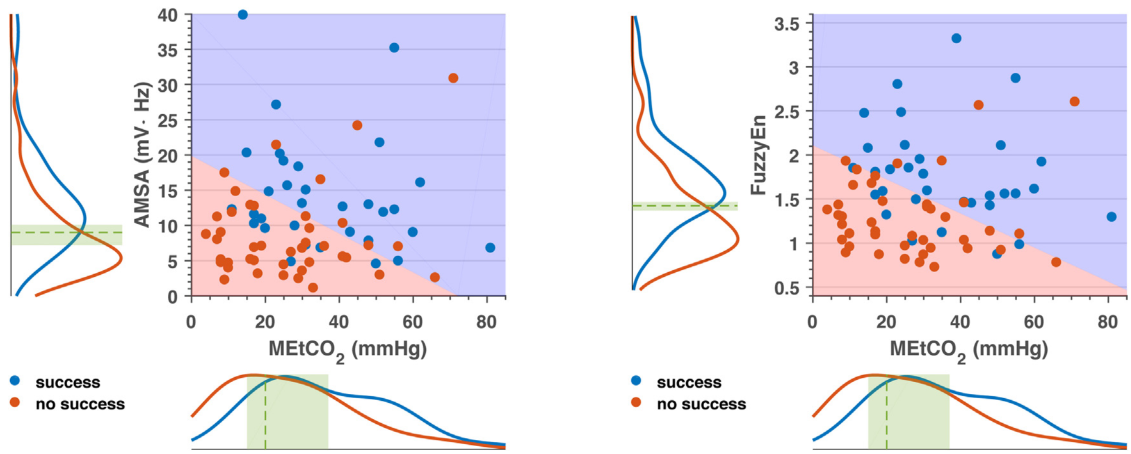

Fig. 4 – Analysis of the models for the prediction of first shock success based on VF-waveform features combined with MEtCO$_2$. The scatter plots show how the pair of values for each shock are distributed, and in both cases successful shocks (blue dots) fall in the north-east side indicating that they correspond to high values of MEtCO$_2$ and the VF-waveform predictor. Unsuccessful shocks (red dots) concentrate in the south-west corner, corresponding to low values of MEtCO$_2$ and the VF-waveform predictor. The blues and red areas are separated by the median decision boundary corresponding to 100 replicas of the logistic regression classifier. The curves on the sides are a non-parametric estimation of the probability distribution of each variable (AMSA left, FuzzyEn right, and MEtCO$_2$ bottom) for successful (blue) and unsuccessful (red) shocks. The dashed green line and area indicate the median (IQR) of the thresholds for 100 replicas, corresponding to AMSA, 9.0 (7.2-10.1) mVHz, FuzzyEn, 1.4 (1.4-1.5), and MEtCO$_2$, 20 (15-37) mmHg, respectively.

expected when different devices and technologies are used. Further analyses are needed to define universal EtCO$_2$ thresholds.

We found an accuracy for the prediction of defibrillation success for first shocks using MEtCO$_2$ (AUC of 0.66) similar to the one reported by Savastano et al.[29] for all shocks (AUC of 0.67). However, our analysis showed that MEtCO$_2$ was not useful as a predictor for all shocks (AUC of 0.54). EtCO$_2$ values may be affected by many factors in recurrent VF and prolonged cardiac arrest, such as quality of CPR, type of CPR (manual/mechanical ventilation and manual/mechanical compressions), ventilation rate, compression site on the sternum or pharmacological treatment.[42,43] In our data, compression and ventilation rates were similar in successful and unsuccessful shocks, but compression depth was significantly larger for unsuccessful shocks. Differences in manual chest compressions may also be associated to rescuer changes, that may affect the position of the hands on the chest and the quality of CPR. For the subgroup of unsuccessful shocks, median MEtCO$_2$ values in all shocks were significantly larger than in first shocks (see Fig. 2), 29 mmHg to 25 mmHg ($p < 0.05$). In Savastano et al.[29] patients were mechanically ventilated and mechanically compressed, so there were no differences in CPR quality, which may explain why MEtCO$_2$ was a predictor of shock success for all shocks. Our findings stress the importance of controlling for additional variables like CPR quality when using MEtCO$_2$ for the prediction of defibrillation success. The effects may be larger for patients with prolonged therapy, i.e. shocks other than the first shock.

VF-waveform analysis is the tool-of-choice for the non-invasive prediction of defibrillation success.[6,8,9,16] The AUCs obtained in this study for AMSA and FuzzyEn are in line with previous findings, which are in the 0.60–0.85 range.[9,12,16,30,44,45] FuzzyEn following the definition introduced in Ref.[17] slightly outperformed AMSA, although the AUCs were very similar. Most importantly, when MEtCO$_2$ had prognostic value, it also added valuable information to the VF-waveform features. For first shocks, the addition of MEtCO$_2$ significantly increased the AUC for AMSA and FuzzyEn, with an increase of 3-points for AMSA and 6-points for FuzzyEn. These results suggest that MEtCO$_2$ could be used as a complementary tool to VF-waveform analysis to predict defibrillation in first shocks, confirming some previous findings with very small datasets.[30] The inclusion of CD in the predictive model produced a smaller increase in AUC of AMSA and no increase for FuzzyEn.

Finally, MEtCO$_2$ was automatically obtained using a capnogram based ventilation detector,[34] and a simple definition of EtCO$_2$ as the maximum CO$_2$ value in the alveolar plateau. When we compared the MEtCO$_2$ values obtained from manual and automatic EtCO$_2$ measurements, we found a median (IQR) error of −1 (−3 to 0) mmHg, and a median unsigned error of 2 (1–4) mmHg. This confirms MEtCO$_2$ can be automatically determined before the shock, and then be used to improve the prediction of defibrillation success in the subgroup of first shocks. The method could therefore be integrated into current monitor-defibrillators that use capnography modules simply adding software.

Limitations

Three were the main limitations of this study. First, the capnogram was not available in the initial shocks of some cases, in which it was introduced once the advanced airway had been placed. Second, the capnogram was acquired using Microstream (sidestream) technology. EtCO$_2$ measurements using other devices or technologies (mainstream, nasal cannulae, etc.) may be slightly different. Third, no information on ROSC after every shock was available, so the criterion to define successful shocks was based on the appearance of sustained QRS complexes in the post-shock interval. This is the most frequently used criterion in the studies on the prediction of shock success.

Conclusions

$MEtCO_2$ was only a predictor of defibrillation success for first shocks, and it added prognostic value to VF-waveform features. The method introduced in this study is the first fully automatic method that combines $MEtCO_2$ values and VF-waveform features for the prediction of defibrillation success.

Conflict of interest

Dr. Idris receives research grants from the US National Institutes of Health (NIH) and serves as an unpaid volunteer on the American Heart Association National Emergency Cardiovascular Care Committee and the HeartSine, Inc. Clinical Advisory.

Dr. Daya has received grant support from the US NIH and has served as an unpaid consultant for Philips Healthcare.

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