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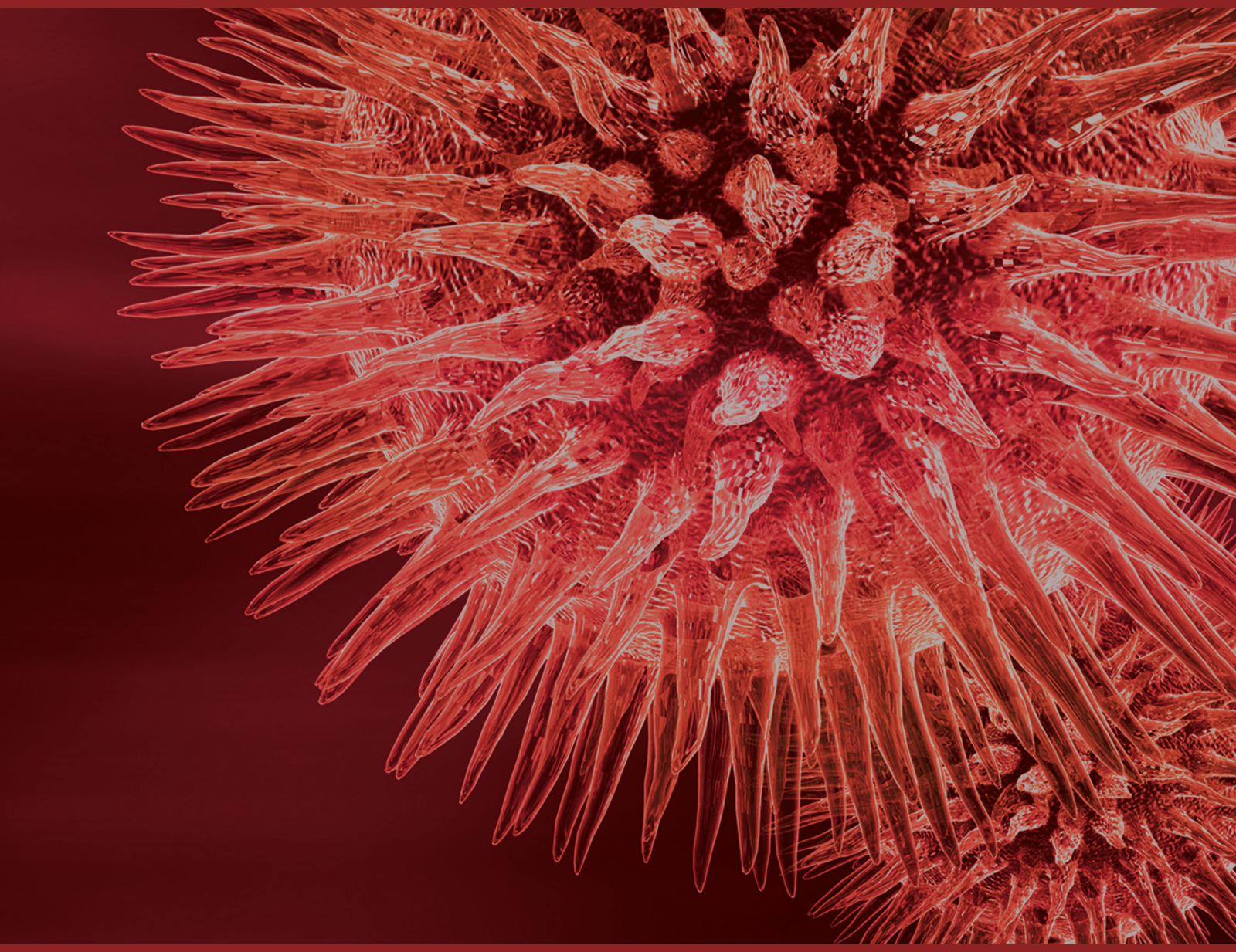
Guest Editors: Giuseppe Ristagno, Tommaso Pellis, and Yongqin Li



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Editorial

Cardiac Arrest and Cardiopulmonary Resuscitation: Starting from Basic Science and Bioengineering Research to Improve Resuscitation Outcome

Giuseppe Ristagno,[1] Tommaso Pellis,[2] and Yongqin Li[3]

[1]*Department of Cardiovascular Research, IRCCS-Institute for Pharmacological Research "Mario Negri", Via La Masa 19, 20156 Milan, Italy*
[2]*Department of Anesthesia and Intensive Care, University Affiliated Hospital "Santa Maria degli Angeli", Via Montereale 24, 33170 Pordenone, Italy*
[3]*School of Biomedical Engineering, Third Military Medical University and Chongqing University, 30 Gaotanyan Main Street, Chongqing 400038, China*

Correspondence should be addressed to Giuseppe Ristagno; gristag@gmail.com

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Cardiovascular disease remains the leading cause of death in the Western world with as many as 350,000 Americans and 700,000 Europeans sustaining cardiac arrest each year. Despite major efforts to standardize cardiopulmonary resuscitation (CPR) interventions, average survival rate presents a large variation all over the world [1–3]. Moreover, besides the initial success of CPR, the majority of victims die within 72 hours, due to the postcardiac arrest syndrome [4].

This difference in successful outcome may be mainly related to the overall diversity and strength in local organizations and algorithms in pre- and postresuscitation care. Indeed, resuscitation is a relatively modern science, although its roots extend back in the centuries. Yet, as early as the 19th century, resuscitation by delivery of an electrical shock was demonstrated. Modern CPR, however, emerged only during the latter half of the 20th century, with the sequence of interventions established in the 1960s under the acronym ABCD: airway, breathing, chest compression, and defibrillation [5]. Since then, novel therapeutic approaches have been conceived, introduced, and tested as new knowledge and pathophysiology understanding of cardiac arrest increased. Nevertheless, due to the complexity and interplay of events occurring during cardiac arrest and after resuscitation, events and mechanisms involved in resuscitation outcome are not completely understood [6]. This special issue on cardiac arrest and CPR, therefore, introduces brilliant contributions from worldwide experts in the field of resuscitation, arising and stimulating new strategies to improve outcome.

More specifically, space was provided to basic research on pathophysiology of cardiac arrest as well as to bioengineering developments. Thus, more clinically relevant and severe models of cardiac arrest, that is, with an underlying acute myocardial ischemia, a condition present in more than 70% of cardiac arrest events, are presented, together with investigations on the role of progressive mitochondrial ischemia during cardiac arrest and a focus on the quality of chest compression as determinant of resuscitation [7, 8]. Bioengineering research is also presented with the introduction of new computerized approaches to ameliorate CPR and postresuscitation care, including an reliable automated cardiac rhythm analysis during chest compression, in order to reduce detrimental interruptions in CPR [9]; an innovative quantitative characterization of early postresuscitation electroencephalogram; and an efficient automatic analysis of data, documentation, and information recorded during resuscitation. Finally, the quality of education and training programs on CPR are other critical factors in improving the effectiveness of resuscitation [10]. Survival rates after

cardiac arrest depend, in fact, not only on the validity and on reliability of guidelines and a well-functioning chain of survival, but also on the quality of education. Thus, a report on a different teaching approach engaging trainees in the assessment of peer performance has been presented.

Translational research is a continuum loop in which basic science discovering is integrated into clinical application, while clinical observations are used to generate scientific topics to be studied by basic science. This integration is extremely important for medicine improvement [11]. Indeed, advances in resuscitation science have improved resuscitation care and ultimately survival of cardiac arrest over the years. The present issue aimed to improve such knowledge although only a limited number of researchers have found the appropriate space. Thus, special journal issues providing visibility to new upcoming idea and hypothesis in resuscitation basic science, translational studies, and bioengineering, like the present issue, have to be supported, paving the way towards a better comprehension of pathophysiology, mechanisms, and management of sudden cardiac arrest and amelioration of resuscitation care.

Giuseppe Ristagno
Tommaso Pellis
Yongqin Li

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Research Article

Effect of Engaging Trainees by Assessing Peer Performance: A Randomised Controlled Trial Using Simulated Patient Scenarios

Charlotte Loumann Krogh,[1] Charlotte Ringsted,[2] Charles B. Kromann,[1] Maria Birkvad Rasmussen,[1] Tobias Todsen,[1] Rasmus Lundhus Jørgensen,[1] Rikke Borre Jacobsen,[3] Jørgen B. Dahl,[3] and Lars Konge[1]

[1] *Centre for Clinical Education (CEKU), University of Copenhagen and Capital Region of Denmark, Rigshospitalet, Teilumbygningen, Blegdamsvej 9, 2100 Copenhagen, Denmark*
[2] *Department of Anesthesia and The Wilson Centre, 200 Elizabeth Street, 1ES-565, Toronto, Ontario, Canada M5G 2C4*
[3] *Department of Anaesthesiology, Centre of Head and Orthopaedics, Rigshospitalet and Copenhagen University, Blegdamsvej 9, 2100 Copenhagen, Denmark*

Correspondence should be addressed to Charlotte Loumann Krogh; charlotteloumann@gmail.com

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Introduction. The aim of this study was to explore the learning effect of engaging trainees by assessing peer performance during simulation-based training. *Methods*. Eighty-four final year medical students participated in the study. The intervention involved trainees assessing peer performance during training. Outcome measures were in-training performance and performance, both of which were measured two weeks after the course. Trainees' performances were videotaped and assessed by two expert raters using a checklist that included a global rating. Trainees' satisfaction with the training was also evaluated. *Results*. The intervention group obtained a significantly higher overall in-training performance score than the control group: mean checklist score 20.87 (SD 2.51) versus 19.14 (SD 2.65) $P = 0.003$ and mean global rating 3.25 SD (0.99) versus 2.95 (SD 1.09) $P = 0.014$. Postcourse performance did not show any significant difference between the two groups. Trainees who assessed peer performance were more satisfied with the training than those who did not: mean 6.36 (SD 1.00) versus 5.74 (SD 1.33) $P = 0.025$. *Conclusion*. Engaging trainees in the assessment of peer performance had an immediate effect on in-training performance, but not on the learning outcome measured two weeks later. Trainees had a positive attitude towards the training format.

1. Introduction

Assessing signs of critical illness is an essential skill for any doctor. While junior doctors often perform the initial assessment of acutely ill patients in hospitals [1] studies have shown that newly qualified doctors are poorly prepared to manage acutely ill patients [2, 3]. Hence, it is desirable to prepare final year medical students for the initial management of emergency situations.

Systematic assessment of critically ill patients using the simple ABCDE mnemonic is widely accepted as a clinical working tool [4]. The ABCDE acronym stands for airway, breathing, circulation, disability, and exposure/environment, describing the order in which the problems associated with acute illness should be addressed. This approach is applicable to all patients, as each step of the algorithm serves to assess signs of critical illness, regardless of the underlying diagnosis.

Undergraduate teaching of acute care is often inconsistent and lacks sufficient practice in core aspects of the ABCDE assessment of critically ill patients [5, 6]. The opportunities for medical students to develop and practise the ABCDE approach in emergency situations are limited. Therefore, simulation-based training that addresses the ABCDE approach may be a suitable alternative that enables trainees

to practise high-risk, low-frequency emergency situations in a safe environment [7, 8]. However, the simulation-based small-group training approach is expensive in terms of utensils, mannequins, and instructors. Therefore, strategies to maximize the learning outcome should be considered.

While active participation of trainees may be an effective learning strategy, it is rarely possible to have the simultaneous participation of all members of a group, which leaves some of the trainees as passive observers. However, research suggests that observation, especially when combined with physical practice, can make a significant contribution to skill learning [9] even when observing "unskilled" demonstrators such as novices [10]. By observing other novices' practice, the trainees are typically engaged in reflection of their own performance rather than imitating the skill. According to Magill, a beneficial strategy could be to provide trainees with a checklist containing key aspects of the skill while observing [10]. The idea behind this strategy is that, under these circumstances, trainees gain a sense of involvement, which enhances motivation and encourages active problem solving and hence may have a positive influence on learning outcome and long-term retention.

The aim of this study was to explore the learning effect of engaging trainees by assessing of peer performance during a simulation-based course in which a critically ill patient was assessed. The trainees' performance was measured by performance outcome during training and two weeks after the course. The study also aimed to explore trainees' reactions to the training format.

2. Methods

This study was a randomised, experimental trial that compared trainees who were engaged in assessment of peer performance to trainees who were not.

2.1. Context of the Study. A four-hour, simulation-based ABCDE training session was developed as part of a three-week emergency medicine course that included faculty-led didactic teaching sessions on a variety of emergency medicine topics and was situated at the end of an undergraduate six-year medical curriculum.

2.2. Study Sample. A sample of eighty-six final year medical students attending the emergency medicine course at Rigshospitalet from 22 May until 13 June 2012 was invited to take part in the study. Eighty-four of the students accepted the invitation and were enrolled in the study. All of the trainees were at the same educational level and comparable in terms of advanced cardiac life support (ACLS) competence. A fee of 400 DKK (approximately 50 Euros) was offered for completing the study. A member of the research group randomly allocated the trainees to either the intervention or the control group using the trainees' participant ID number and randomisation sequences as well as tables created using http://www.random.org/. In both groups, the sequence of roles within the team was also part of the randomisation process.

2.3. Ethics. The study protocol was submitted to the Danish Bioethics Committee for the Capital Region, Copenhagen, Denmark, which waived the requirement for full ethical approval (protocol number: H-4-2012-060). Participants were informed about the purpose of the study and ensured anonymity, and individual written consents were collected.

2.4. ABCDE Training. The ABCDE training, including an ABCDE template (Figure 2), was designed by the research group comprising anaesthesiologists and faculty from the Centre for Clinical Education (CEKU). The ABCDE template was introduced during the first session of the emergency medicine course.The simulation-based ABCDE training session comprised an introduction by the facilitator, a video demonstration of the application of the ABCDE principles, and subsequent training on six detailed, megacode scenarios, each of which had an intended duration of 12 minutes. The cases addressed both medical and surgical conditions frequently seen in emergency departments but did not include any trauma cases. The simulation sessions were conducted in groups of six trainees on a Resusci-Anne mannequin (Laerdal Medical Corporation, Stavanger, Norway). Each group performed six scenarios facilitated by the same faculty member from CEKU. Each scenario had three active roles—a team leader and two helpers—while the rest of the group were observers. The six trainees took turns assuming these roles. All scenarios were videotaped for subsequent assessment. While facilitating the scenarios, the facilitator assessed the performances of all team leaders using a checklist scoring form (Table 2). The content of the checklist was very similar to the ABCDE template provided to all trainees at the first session of the emergency medicine course. The design of the checklist scoring form was inspired by the advanced life support Cardiac Arrest Scenario (CAS) test checklist. In addition to the checklist items, the scoring form included an overall global rating (scale 1–5), where a score ≥ 3 indicated acceptable overall performance.

After each scenario, the facilitator provided postsimulation debriefing, supplemented by comments from the peer observers; however, detailed results of the assessment were not provided.

2.5. Intervention Conditions. The intervention group underwent the same ABCDE training as the control group. However, peer observers of the intervention group were asked to assess the team leader's performance during each scenario using the same checklist scoring form as the facilitator. At the end of each scenario, the scoring forms of the peer observers were collected. The team leader was not informed of his/her performance score.

2.6. Evaluation and Retention Test. After the ABCDE training, the trainees answered a single evaluation question about their satisfaction with the training format; this was measured using a seven-point Likert scale. Finally, two weeks after the course, all trainees were invited to participate in the assessment of their performance. During these two weeks, the trainees did not have any further clinical or theoretical

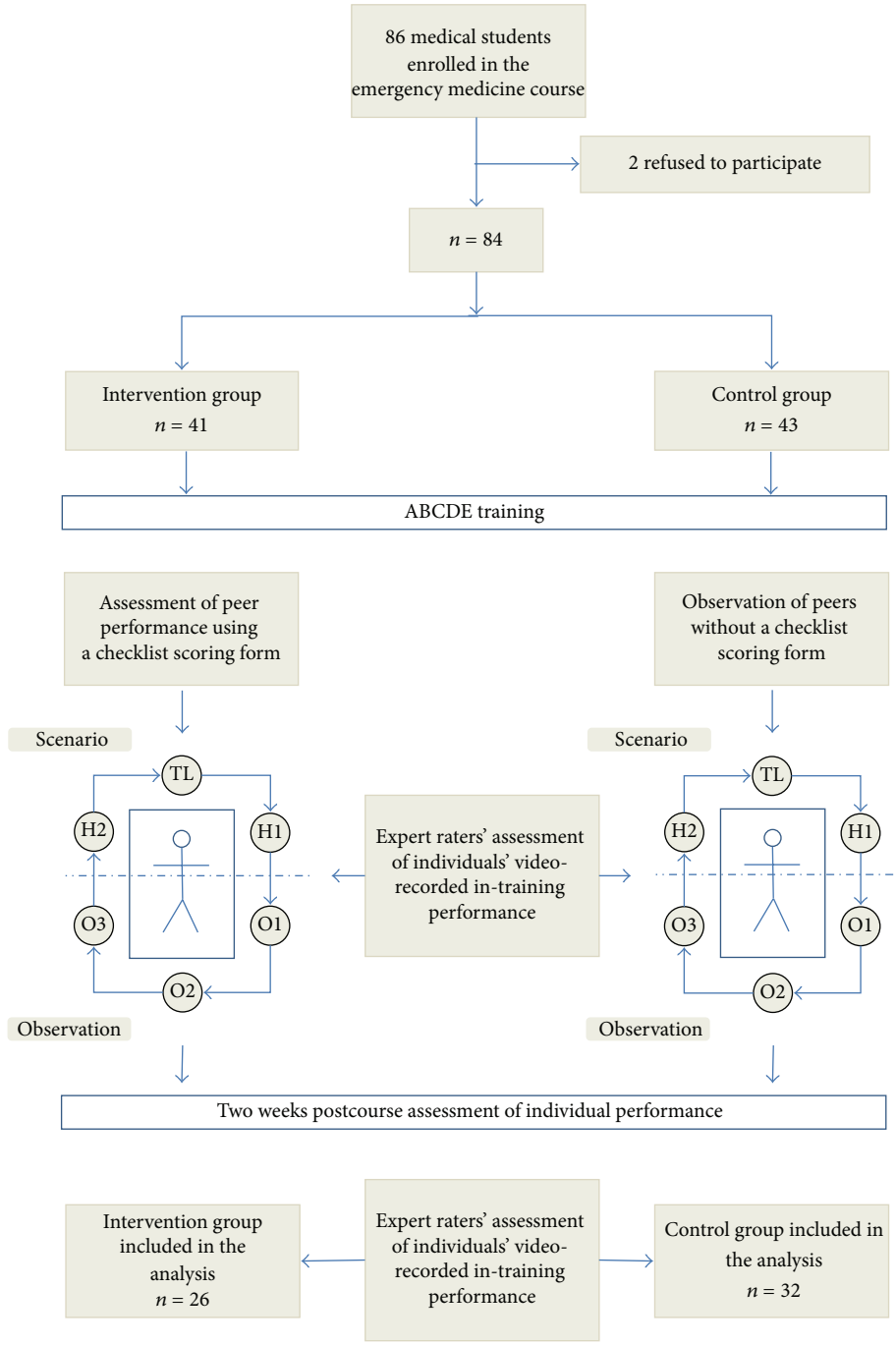

Figure 1: Flow chart showing the study design. Eighty-fourfinal year medical students were placed randomly into either the intervention group or the control group. Observers of the intervention group assessed the team leader's performance using a checklist scoring form. All participants were invited to participate in the assessment of performance two weeks after the course. Trainees' performances, in-training as well as after the course, were videotaped and assessed by two expert raters.

training, as the course was carried out at the conclusion of their time at the medical school. The trainees completed the performance test individually, assuming the role as team leader, and the facilitators acted as helpers. The performance test scenario was different in content but similar to the structure of the ABCDE training scenarios. As with the ABCDE training scenarios, the performance test scenario was videotaped for subsequent assessment. The study design is illustrated in Figure 1.

2.7. Outcome Measurements. This study included two outcome measures: the trainees' in-training performance and the trainees' individual performance assessed two weeks after the ABCDE training (retention test).

Assessments of performances were based on the video recordings obtained during training and at the retention test. For this purpose, all the videos were edited to show only the simulation sessions; the debriefings, introduction to the scenarios, and the like were edited out.

The video-recorded performances of the team leaders were assessed by two trained independent and trained raters with experience in advanced life cardiac support (ALCS) teaching and testing. The raters were blinded with regard to whether they were assessing the intervention group or the control group. The raters used the same checklist scoring form as that used by the facilitator and peer observers of the intervention group during the ABCDE training.

2.8. Statistical Analysis. Interrater reliability was examined using the intraclass-correlation coefficient. An average of the raters' scorings was used to compare the intervention and control groups. An independent sample t-test was used to compare the groups regarding overall in-training performance and performance on the retention test. The two groups were also compared regarding checklist scores, global ratings, and satisfaction with the training format. Data were analysed using the PASW statistical software package version 19.0 (SPSS Inc., Chicago, Illinois, USA). P values < 0.05 were considered statistically significant.

3. Results

Eighty-four out of the 86 trainees agreed to participate and all 84 completed the ABCDE training.

Interrater reliability was high on both the checklist score and the global rating (ICC = 0.83 and 0.79, resp.).

The intervention group obtained a significantly higher overall in-training performance score than the control group: mean checklist score of 20.87 (SD 2.51) versus 19.14 (SD 2.65) $P = 0.003$ and mean global rating of 3.25 SD (0.99) versus 2.95 (SD 1.09) $P = 0.014$.

Students' evaluation of the training format was significantly higher in the intervention group: mean rating of 6.36 (SD 1.00) versus 5.74 (SD 1.33) in the control group, $P = 0.025$.

The dropout rate at the retention test was rather high in both groups: 15 participants (37 percent) in the intervention group and 11 participants (26 percent) in the control group, $P = 0.64$.

The learning outcome, assessed two weeks after the course, showed no significant difference between the two groups, regarding either checklist scores ($P = 0.923$) or global ratings ($P = 0.322$) (Table 1).

4. Discussion

This study has demonstrated that engaging trainees in structured assessment of their peers during observational phases in a simulation-based ABCDE training session had a positive effect on in-training performance. Through a simultaneous combination of observation and assessment of peer performance, the trainees of the intervention group were offered the opportunity to extract features of the performance in order to guide and develop their own performance of the skill [10]. However, the results of the retention test demonstrated no significant difference between the two groups.

Students' attitudes towards assessment of peer performance highly endorsed the concept of active observation during ABCDE training. Assessment of peer performance has been increasingly adopted at a number of levels in the education of healthcare professionals [11, 12]. Introducing assessment of peer performance in undergraduate medical education may offer insights into the students' work habits and those of their peers, which could foster motivation and reflection of personal and professional competences. Additional advantages of assessment of peer performance include familiarisation with peer review from colleagues and promotion of future learning and professional development [13].

A phenomenon known as test-enhanced learning could be relevant to this study. Test-enhanced learning implies that being tested will enhance the long-term retention of knowledge or skills. Hence, being tested in itself should affect long-term retention positively [14, 15]. Kromann et al. investigated testing as part of a simulation-based resuscitation course and found a significant higher learning outcome in the intervention group, indicating that testing, in itself, may be an effective strategy to increase learning outcome [15].

Observation, combined with simultaneous assessment of peer performance, could generate a sense of a "testing effect." However, in our experimental setup both the intervention group and the control group were tested during the training (e.g., the facilitator used the checklist scoring form during scenario training in both groups, video recordings of all scenarios, etc.). This meant that we were not able to investigate the effect of testing.

Using e-learning programs could be a feasible strategy to prolong retention after simulation-based skill courses. However, Jensen et al. found that e-learning had no significant effect as a booster to maintain competences following an advanced life support (ALS) course. The lack of social interaction was identified as the major cause predicting the use of e-learning [16]. Future studies that combine tests with e-learning could demonstrate prolonged retention of skills obtained in a simulated setting.

DeMaria et al. found that participants exposed to emotional stress demonstrated greater anxiety, which correlated with increased ACLS scores measured six months after the course [17]. The participants of our study were exposed to continuous assessment and video recording, which could have generated emotional stress; however, no objective measurement of this aspect was conducted.

One strength of this study is measuring learning outcomes two weeks after the course (retention test). Potential improvements in learning measured by later tests are in accordance with general recommendations for evaluation of skill learning, that is, to test learning outcomes after a pause in training (retention of learning) in order to prove sustainable skills [18]. Furthermore, using two raters with experience in ALS training and assessment of skills ensured reliable ratings.

This study has certain limitations. The study includes a risk of selection bias, as it is usually the most competent

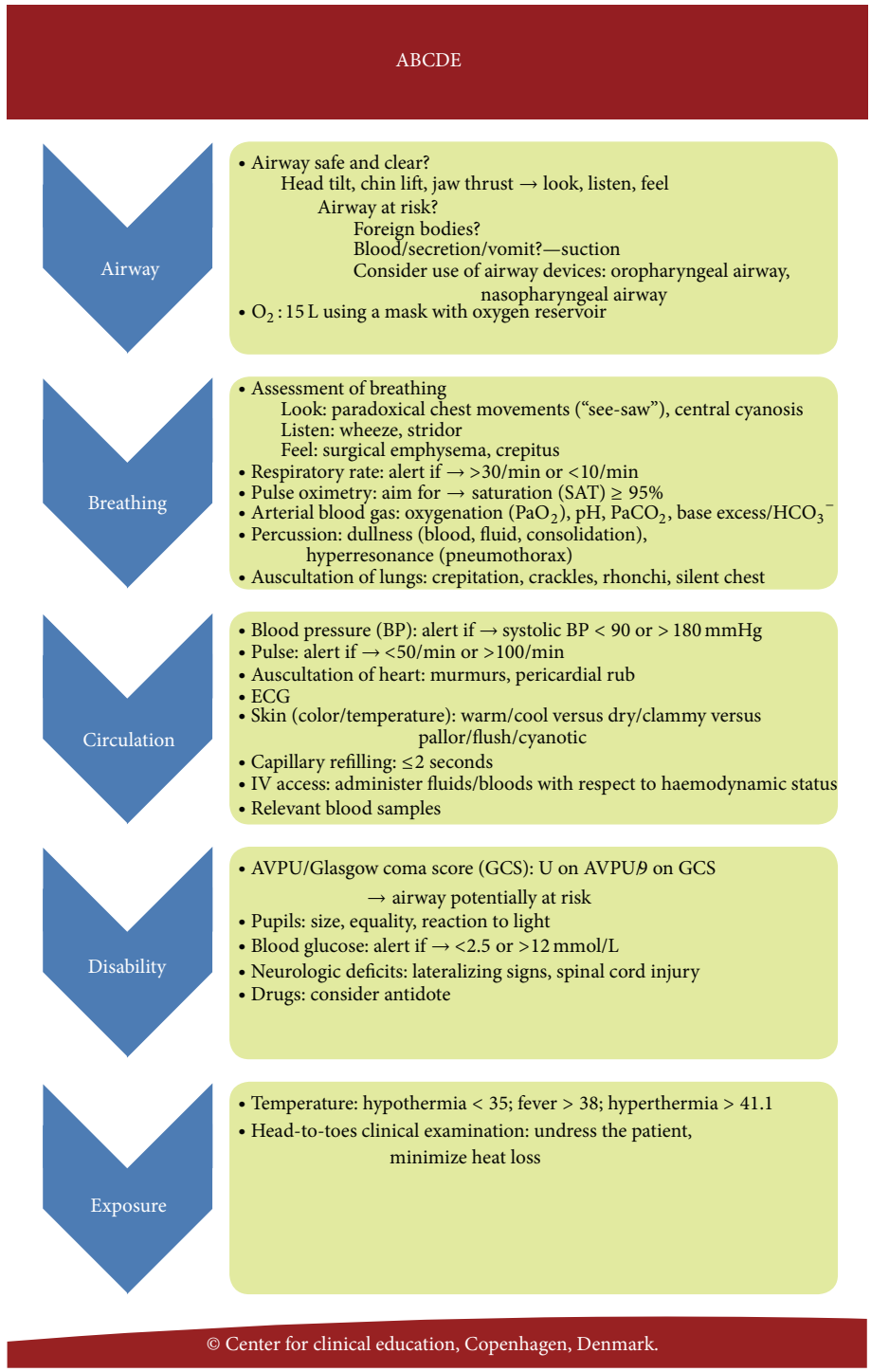

Figure 2: The ABCDE template describing the order in which the problems associated with acute illness should be addressed.

students who volunteer for educational studies. Having said that, almost 97 percent of the sample volunteered to participate. There is also a risk of selection bias due to the fee for participating in the study. However, the randomised design and the relatively large sample aimed to minimise selection bias. Furthermore, the dropout rate was almost similar in both groups, despite the reward. The high dropout rate could possibly be explained by a lack of motivation due to the fact that the trainees had just qualified as doctors and might not have felt the need for any additional training.

The students in the intervention group rated the training format higher than the control group and hence engaging students in peer assessment during ABCDE training may represent a valuable addition. However, future research is

Table 1: Performance of the intervention group compared with performance of the control group measured as in-training performance and performance two weeks post-course.

In-training performance	Intervention group $N = 41$ Mean (SD)	Control group $N = 43$ Mean (SD)	P-value
Checklist scores	20.87 (SD 2.51)	19.14 (SD 2.65)	0.003
Global rating	3.52 (SD 0.99)	2.95 (SD 1.09)	0.014
Two weeks post-course performance	$N = 26$ Mean (SD)	$N = 32$ Mean (SD)	P-value
Checklist scores	19.90 (SD 2.89)	19.84 (SD 1.75)	0.923
Global rating	3.52 (SD 0.98)	3.73 (SD 0.65)	0.322

Definition of abbreviations: SD: standard deviation.

Table 2: The checklist scoring form. The intervention group used the checklist to assess peer performance during the observational phases. In addition, the facilitator and the two raters assessing in-training performance and performance two weeks post-course used the same checklist.

	A—Airway	Tick the box if performed
1	Assess if the airway is open (patient talks/has normal respiration)	
2	Ask helper to apply Hudson mask with reservoir and connect 10–15 L O2	
	B—Breathing	Tick the box if performed
3	Assess respiration (looks, listens, feels)	
4	Ask for respiratory frequency	
5	Ask helper to apply pulse oximetry	
6	Perform auscultation of the lungs	
	C—Circulation	Tick the box if performed
7	Ask helper to perform blood pressure measurement	
8	Ask helper to assess central pulse	
9	Ask helper to measure ECG	
10	Assess the skin: color/temperature	
11	Assess capillary response	
12	Perform auscultation of the heart	
13	Ask helper to do a intravenous canulation	
14	Ask helper to do an ABG	
15	Ask helper to take out blood samples	
	D—Disability	Tick the box if performed
16	Assess if the patient is concious (AVPU/GCS)	
17	Assess and estimate size of pupiles	
18	Ask for blood sugar value.	
19	Examine motor function of limbs	
	E—Exposure/Enviroment	Tick the box if performed
20	Ask helper to measure temperature	
21	Head-to-toe examination	
	Analysis	Tick the box if performed
22	Summary of ABCDE assessment	
23	Correct analysis of ABG	
	Diagnostics and treatment	Tick the box if performed
24	Propose relevant diagnosis	
25	Outline clinical course	
	Global rating:	Scale: 1–5 (Acceptable ≥ 3)
	Overall assessment of team leader's performance	

Definition of abbreviations:
ECG: electrocardiogram.
ABG: arterial blood gas.
AVPU: Alert, Verbal, Pain and Unconsious.
GCS: Glascow Coma Scale.

required to investigate how and if the assessment of peer performance during ABCDE training enhances knowledge and understanding and long-term learning outcome.

5. Conclusions

Engaging trainees in the assessment of peer performance using a checklist scoring form during observational phases in a four-hour, simulation-based ABCDE training course had an immediate effect on in-training performance but not on learning outcome measured two weeks later. In addition, trainees had a positive attitude towards assessment of peer performance.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

A Reliable Method for Rhythm Analysis during Cardiopulmonary Resuscitation

U. Ayala,[1] U. Irusta,[1] J. Ruiz,[1] T. Eftestøl,[2] J. Kramer-Johansen,[3] F. Alonso-Atienza,[4] E. Alonso,[1] and D. González-Otero[1]

[1] *Communications Engineering Department, University of the Basque Country UPV/EHU, Alameda Urquijo S/N, 48013 Bilbao, Spain*
[2] *Department of Electrical Engineering and Computer Science, Faculty of Science and Technology, University of Stavanger, 4036 Stavanger, Norway*
[3] *Norwegian Centre for Prehospital Emergency Care (NAKOS), Oslo University Hospital and University of Oslo, 0424 Oslo, Norway*
[4] *Department of Signal Theory and Communications, University Rey Juan Carlos, Camino del Molino S/N, 28943 Madrid, Spain*

Correspondence should be addressed to U. Irusta; unai.irusta@ehu.es

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Interruptions in cardiopulmonary resuscitation (CPR) compromise defibrillation success. However, CPR must be interrupted to analyze the rhythm because although current methods for rhythm analysis during CPR have high sensitivity for shockable rhythms, the specificity for nonshockable rhythms is still too low. This paper introduces a new approach to rhythm analysis during CPR that combines two strategies: a state-of-the-art CPR artifact suppression filter and a shock advice algorithm (SAA) designed to optimally classify the filtered signal. Emphasis is on designing an algorithm with high specificity. The SAA includes a detector for low electrical activity rhythms to increase the specificity, and a shock/no-shock decision algorithm based on a support vector machine classifier using slope and frequency features. For this study, 1185 shockable and 6482 nonshockable 9-s segments corrupted by CPR artifacts were obtained from 247 patients suffering out-of-hospital cardiac arrest. The segments were split into a training and a test set. For the test set, the sensitivity and specificity for rhythm analysis during CPR were 91.0% and 96.6%, respectively. This new approach shows an important increase in specificity without compromising the sensitivity when compared to previous studies.

1. Introduction

Out-of-hospital cardiac arrest (OHCA) is a leading cause of mortality in the industrialized world, with an estimated annual incidence between 28 and 55 cases per 100,000 person-years [1]. Early cardiopulmonary resuscitation (CPR) and early defibrillation are the key interventions for survival after cardiac arrest [2]. Defibrillation may be administered by an automated external defibrillator (AED), which incorporates a shock advice algorithm (SAA) that analyzes the ECG to detect shockable rhythms. Current CPR guidelines emphasize the importance of high quality CPR with minimal interruptions in chest compressions (CCs) [3]. However, CPR must be interrupted for a reliable rhythm analysis because CCs produce artifacts in the ECG. These interruptions adversely affect the probability of defibrillation success and subsequent survival [4]. Currently, CPR is interrupted every 2 minutes for rhythm reassessment on an artifact-free ECG.

Although different approaches to rhythm analysis during CPR have been explored, for instance, algorithms that directly diagnose the ECG corrupt with CPR artifacts [5, 6], filtering the CPR artifact has been a major approach (see [7] for a comprehensive review). The time-varying characteristics of the CPR artifact and its spectral overlap with both shockable and nonshockable cardiac arrest rhythms mandate the use of adaptive filters [8], which use reference signals to model the CPR artifact. Over the years, many solutions have been proposed, including Wiener filters [9], Matching Pursuit Algorithms [10], Recursive Least Squares [11], least mean squares (LMS) [12], or Kalman filters [13, 14]. Adaptive solutions using exclusively the ECG have also been explored [15, 16], but the results were poorer. To evaluate

the performance of these methods, researchers first filtered the CPR artifact and then analyzed the rhythm using a SAA to obtain the sensitivity and specificity of the method, that is, the proportion of correctly diagnosed shockable and nonshockable rhythms, respectively. However, the SAAs used were originally designed to analyze artifact-free ECG instead of the ECG after filtering.

Currently rhythm analysis during CPR is not possible [17]. Most methods have sensitivity above 90%, the minimum value recommended by the American Heart Association (AHA) for SAA on artifact-free ECG [18]. However, specificity rarely exceeds 85%, well below the 95% value recommended by the AHA. A low specificity would result in a large number of false shock diagnoses during CPR, which would unnecessarily increase the number of interruptions in CPR. Overall, the main cause of the low specificity is filtering residuals in nonshockable rhythms. These residuals frequently resemble a disorganized rhythm [10, 12] and are often misdiagnosed as shockable by SAAs designed to analyze artifact-free ECG. This problem is more prominent when the electrical activity of the underlying heart rhythm is low, particularly for asystole (ASY) [14, 16], because filtering residuals may have amplitudes comparable or larger than those of the underlying ECG.

In this study we explore the possibility of combining adaptive filtering techniques with a SAA designed to optimally classify the rhythm after filtering. The aim is to improve the accuracy of current approaches and in particular to overcome the low specificity. When compared to previous studies, our results showed an increased specificity without compromising the sensitivity, for a comprehensive dataset of OHCA rhythms.

2. Materials and Methods

2.1. Data Collection. The data for this study were extracted from a large prospective study of OHCA conducted between 2002 and 2004 in three European sites [21, 22]. CPR was delivered by trained ambulance personnel in adherence to the 2000 resuscitation guidelines. Episodes were recorded using modified Laerdal Heartstart 4000 defibrillators (4000SP) and an external CPR assist pad to acquire additional reference signals. All signals were acquired with a 500 Hz sampling rate. The initial rhythm and all subsequent changes in rhythm were annotated by consensus of an experienced anesthesiologist and a biomedical engineer, both specialized in resuscitation [21, 22]. Rhythm annotations comprised five types (see [21] for further details): VF and fast ventricular tachycardia (VT) in the shockable category and ASY, pulseless electrical activity (PEA), and pulse-generating rhythm (PR) in the nonshockable category. Intervals with chest compressions were annotated using the compression depth (CD) obtained from the CPR assist pad.

For this study specific records containing the ECG and CD signals were automatically extracted from the original episodes. First rhythm transitions were identified using the original annotations, and then for each interval without rhythm transitions at most one record was extracted to avoid bias due to data selection. Records were extracted if the following criteria were met: duration of more than 20-s, ongoing CCs, and the same rhythm annotation before and after CCs. Following the AHA statement the records were grouped into a shockable and a nonshockable category. The amplitude thresholds adopted for coarse VF and ASY are those accepted in the literature on SAAs [6, 18]. The following criteria and rhythm definitions were checked in the clean intervals before and after CCs.

Shockable Rhythms. This category includes fast VT, with rate above 150 beats per minute (bpm), and coarse VF. Coarse VF was defined as VF with peak-to-peak amplitude above 200 μV and a fibrillation frequency above 2 Hz.

Nonshockable Rhythms. These rhythms were further divided into the following:

(i) organized rhythms (ORG): all nonshockable rhythms except ASY (PEA and PR),

(ii) asystole (ASY): rhythms with peak-to-peak amplitudes below 100 μV for at least 2-s.

All signals were resampled to $f_s = 250$ Hz, a sampling rate similar to that used by commercial AEDs. In what follows, the sample index and time variables are related by $t = n \cdot T_s$ ($T_s = 1/f_s$). The ECG was band limited to 0.5–30 Hz (order 10 Butterworth filter), a typical ECG monitor bandwidth used in AEDs [5, 6], which removes base line wander and high frequency noise.

Following standard practice in SAA design, the rhythm analysis method was designed to analyze three consecutive 3 s windows, so it gives a diagnosis every 9 s [23, 24]. A 3 s window is sufficient to characterize the rhythm in terms of rate, stability, and morphology and to make a shock (Sh) or no-shock (NSh) decision [23]. SAA algorithms combine several consecutive diagnoses to avoid errors due to rhythm transitions and to avoid shock diagnoses for short bursts of nonsustained VT. Therefore, each record was divided into nonoverlapping 9 s segments. The 9 s segments were randomly split into two separate sets, one to train the algorithm and an independent set to test the algorithm, as required by the AHA statement. In addition we made sure that the patients on both sets were different (AHA statement) and that the distribution of rhythm types was similar in both sets.

2.2. Rhythm Analysis Method. The block diagram of the rhythm analysis method is shown in Figure 1. First, a CPR artifact suppression filter estimates the underlying rhythm, that is, the filtered ECG signal, s_{filt}. Then, a SAA diagnoses every 3 s window of the filtered signal. The SAA is designed to optimally classify the filtered signal and is further composed of two sequential subalgorithms: (1) a detector of rhythms with low electrical activity (LEA), that is, nonshockable rhythms without distinguishable QRS complexes such as ASY or idioventricular rhythms, and (2) a Sh/NSh algorithm that classifies windows with electrical activity as shockable or nonshockable.

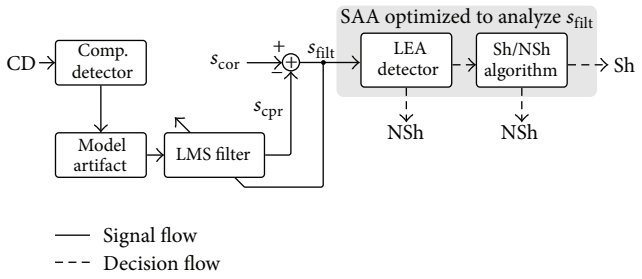


Figure 1: Block diagram of the new approach to rhythm analysis during CPR in which an adaptive filter (LMS filter based on the CD signal) is used in combination with a SAA designed to optimally classify the filtered signal, s_{filt}.

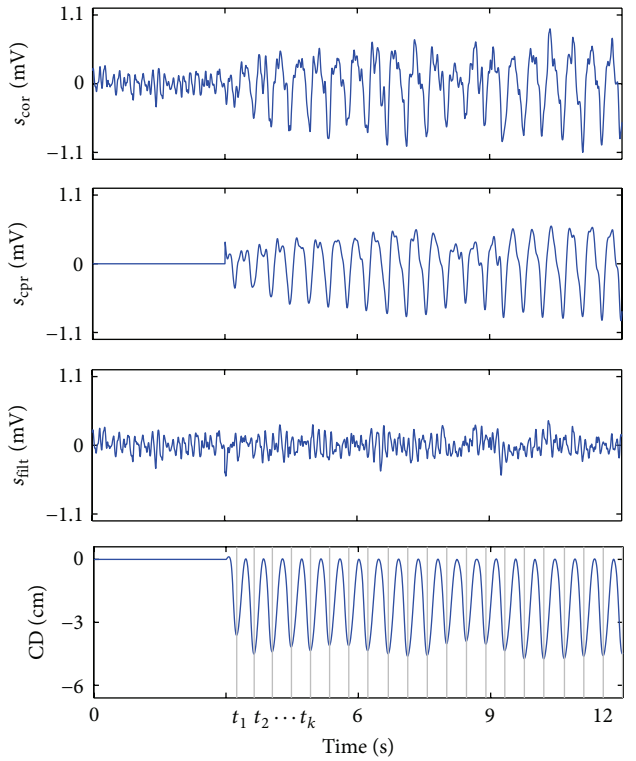


Figure 2: Filtering example of a 12-s segment. In the first 3 s there is no artifact and the underlying VF is visible. The filter estimates the artifact, s_{cpr}, using information derived from the CC marks, indicated by vertical lines in CD (t_k instants).

2.3. Chest Compression Artifact Filter. CPR artifacts were suppressed using a state-of-the-art method based on an LMS filter [12]. In this method, CC artifacts are modeled as a quasiperiodic interference with a time-varying fundamental frequency, $f_o(n)$, which is the instantaneous frequency of the CCs. This frequency is derived from the t_k instants, the CC marks shown in Figure 2. The LMS algorithm adaptively estimates the time-varying amplitudes, $c_k(n)$, and phases, $\phi_k(n)$, of the first 5 harmonics of the artifact by fitting the following model:

$$s_{cpr}(n) = \sum_{k=1}^{5} c_k(n) \cos\left(k \cdot 2\pi f_o(n) \cdot n + \phi_k(n)\right), \quad f_o(n) = \frac{1}{t_k - t_{k-1}} \quad \text{for } t_{k-1} \le nT_s < t_k. \tag{1}$$

In summary, the LMS algorithm dynamically estimates the CPR artifact by adaptively estimating its harmonic content. For this study, we used the optimal values of the filter parameters as described in [12, 19]. As shown in Figure 1, the filtered signal was obtained by subtracting the estimated CPR artifact from the corrupted ECG. Figure 2 shows those signals for a 12-s segment with an underlying VF rhythm.

2.4. Shock Advice Algorithm. The SAA consists of a LEA detector followed by the Sh/NSh algorithm. The LEA detector identifies LEA windows as nonshockable; the rest of the windows are further processed by the Sh/NSh algorithm for a definitive diagnosis.

2.4.1. LEA Rhythm Detector. Some nonshockable rhythms (ASY, bradyarrhythmias or idioventricular rhythms) may not present QRS complexes in a 3 s analysis window. In these cases, filtering the CC artifact results in s_{filt} with low amplitudes and short intervals in which the electrical activity is very low (see Figure 3(a)). To further improve LEA detection s_{filt} was high pass filtered with a 2.5 Hz cut-off frequency using an order 5 Butterworth filter, which removed slow fluctuations of the ECG in LEA rhythms but preserved most frequency components of VF, as shown in Figure 3. The resulting signal, s_{LEA}, was used to obtain the following two features:

(i) P_{LEA}: energy of s_{LEA} in the 3 s window:

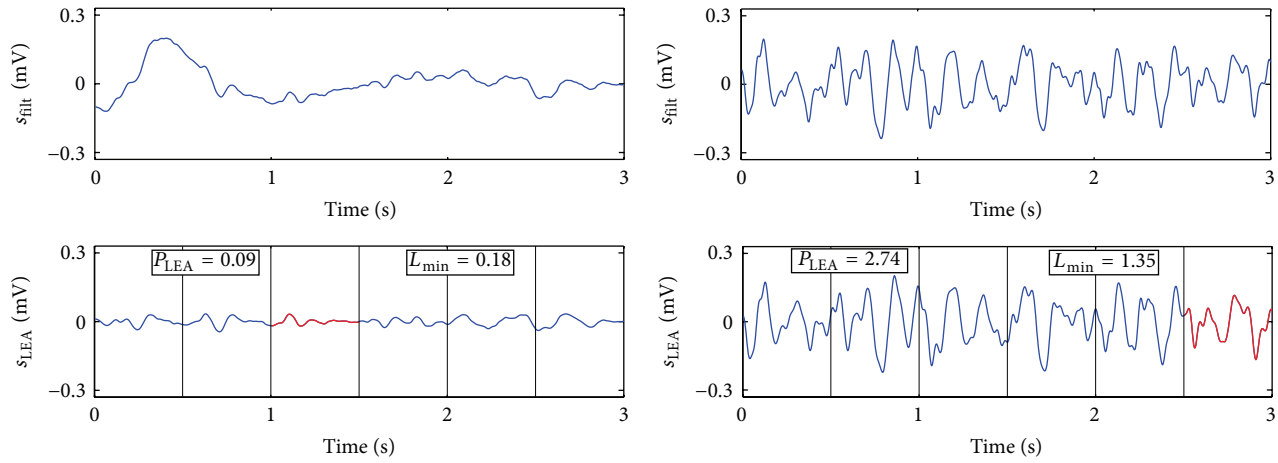
$$P_{LEA} = \sum_{n} s_{LEA}^2(n); \tag{2}$$

(ii) L_{min}: minimum of the curve lengths of s_{LEA} for nonoverlapping 0.5-s intervals, which measures the minimum electrical activity in 0.5-s intervals. In discrete form, the curve length of the kth subinterval is [25]

$$L_k = \sum_{n=kf_s/2+1}^{(k+1)f_s/2} \sqrt{\Delta s_{LEA}^2(n) + T_s^2}, \tag{3}$$

where Δs_{LEA} is the first difference of s_{LEA}.

LEA rhythms have smaller values of P_{LEA} and L_{min} than shockable rhythms, as shown in Figure 3. This block was designed as a detector; that is, it gives a NSh diagnosis if a LEA rhythm is detected; otherwise the window is further processed by the Sh/NSh algorithm.



(a) ASY (b) VF

FIGURE 3: Examples of a LEA rhythm (a) and a VF (b) window after filtering the CC artifact, s_{filt}, and preprocessed to suppress components under 2.5 Hz, s_{LEA}. Vertical lines separate the 0.5 subintervals, and the one with lowest activity (L_{min}) is shown in red.

2.4.2. Sh/NSh Algorithm. During resuscitation, ORG rhythms with electrical activity may be very different in terms of rate, QRS width, or QRS morphology. Furthermore, even after CPR artifact suppression, rhythms may present important filtering residuals that may resemble VF. Four features derived from the frequency domain and slope analyses were defined. For rhythms with electrical activity, these features emphasize the differences between nonshockable (with QRS complexes) and shockable (without QRS complexes) rhythms.

2.4.3. Slope Analysis Features. QRS complexes were enhanced in s_{filt} by computing the moving average of the square of its first difference (its slope):

$$d_{filt}(n) = \frac{1}{N}\sum_{k=0}^{N-1}\left(s_{filt}(n-k) - s_{filt}(n-k-1)\right)^2, \quad (4)$$

where N corresponds to the number of samples in a 100 ms interval. Then, d_{filt} was divided by its maximum value in the analysis window to obtain $\overline{d_{filt}}$. As shown in Figure 4, in ORG rhythms $\overline{d_{filt}}$ is large only around QRS complexes and very small otherwise, whereas in VF the values of $\overline{d_{filt}}$ are more evenly distributed and present many peaks. Two features were defined to measure these differences:

(i) bS: slope baseline, a measure of how concentrated slope values are around small values (baseline), computed as the 10th percentile of $\overline{d_{filt}}$,

(ii) nP: number of peaks above a fixed threshold in $\overline{d_{filt}}$.

Shockable rhythms will present larger values of bS and nP as shown in Figure 4.

2.4.4. Frequency Domain Features. For the frequency analysis, a Hamming window was applied to s_{filt} and its zero padded 1024-point FFT was computed. The power spectral density was estimated as the square of the magnitude of the FFT and normalized to total power of one to give $P_{ss}(f)$. As shown in Figure 5, VF concentrates most of its power around the fibrillation frequency, whereas ORG rhythms may have important power content at higher frequencies, on the harmonics of the heart rate. Two discrimination features were defined, with limiting frequencies in line with the characteristics of human VF [26, 27]:

(i) P_{fib}: power proportion around the VF-fibrillation band (2.5–7.5 Hz),

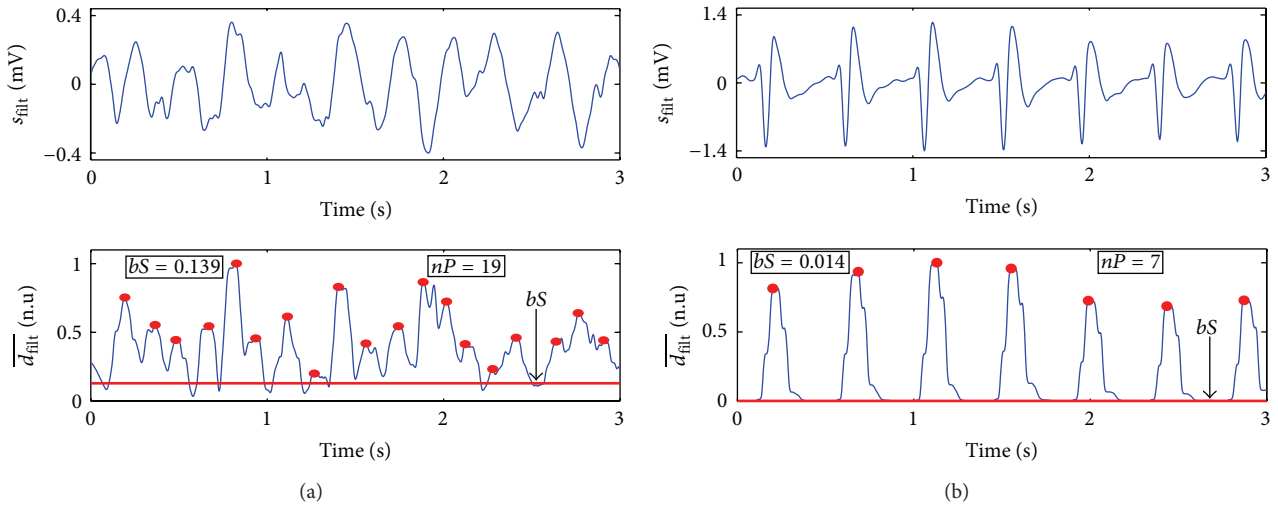
(ii) P_h: power proportion in the high spectral bands (above 12 Hz).

Shockable rhythms have larger values of P_{fib} but lower values of P_h (see Figure 5).

2.4.5. Support Vector Machine (SVM) Classifier. The Sh/NSh algorithm classified windows using a SVM with a Gaussian kernel [28]. First, features were standardized to zero mean and unit variance using the data in the training set. These $\mathbf{x}_i$ vectors of four normalized features were arranged as $\{(\mathbf{x}_1, y_1), \ldots, (\mathbf{x}_n, y_n)\} \in \mathbb{R}^4 \times \{\pm 1\}$, where $y_i = 1$ for shockable and $y_i = -1$ for nonshockable windows. After training, the discriminant function for a window with feature vector $\mathbf{x}$ is

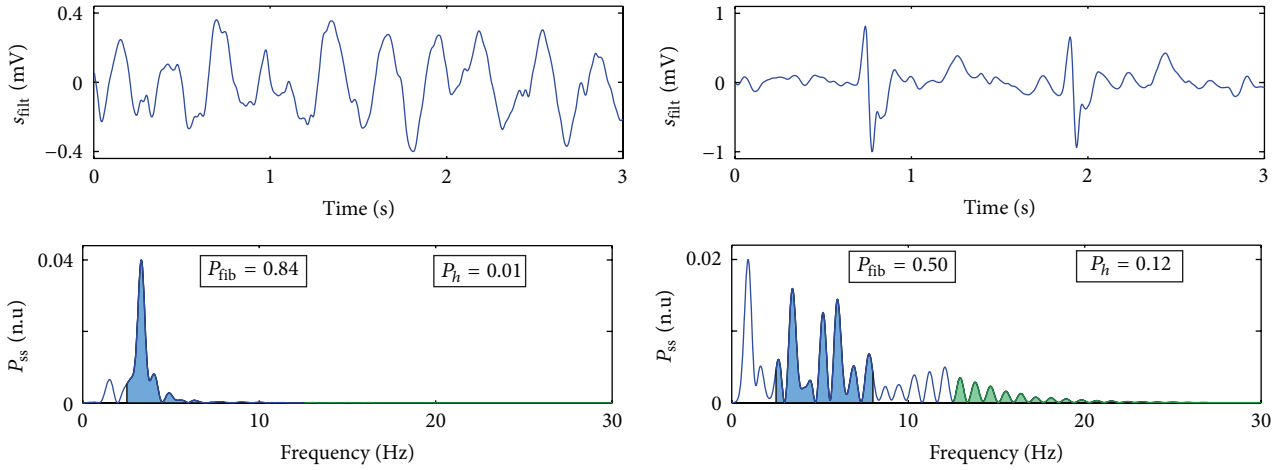
$$f(\mathbf{x}) = \sum_{i=1}^{N_s} \alpha_i y_i \exp\left(-\gamma \left\|\mathbf{x} - \mathbf{x}_i\right\|^2\right) + b, \quad (5)$$

where $\mathbf{x}_i$ are the support vectors, N_s is the number of support vectors, and α_i and b are coefficients estimated during training. Windows were classified as shockable for $f(\mathbf{x}) > 0$ or nonshockable for $f(\mathbf{x}) \leq 0$. Selecting an optimal SVM model for the classification problem involves selecting two parameters: C and γ. The width of the Gaussian kernel, γ, determines the flexibility of the decision boundary [28]. The soft margin parameter, C, is used exclusively in the optimization process and is a tradeoff between classification



(a) (b)

FIGURE 4: Example of the slope analysis for VF (a) and an ORG (b) window. During VF the slope, $\overline{d_{\text{filt}}}$, is irregular with many peaks, whereas ORG rhythms are regular with fewer peaks and concentrate most $\overline{d_{\text{filt}}}$ values around the baseline.



(a) VF (b) ORG

FIGURE 5: Example of the frequency domain analysis for VF (a) and an ORG (b) window. VF concentrates most of its power around the fibrillation band (blue). ORG rhythms have a spectrum with many harmonics of the heart rate and thus larger P_h (in green).

errors in training data and separating the rest of the training data with maximum margin [28].

2.5. Data Analysis and Algorithm Optimization. The rate and depth characteristics of CPR in our data were analyzed for each 9 s segment. The distributions for rate and depth did not pass the Kolmogorov-Smirnov test for normality and are reported as median and 5–95 percentiles.

For each discrimination feature of the SAA, statistical differences in medians between the targeted classification groups of each subalgorithm were measured using the Mann-Whitney U test. The optimization process was carried out for the 3 s windows of the training set in two sequential steps.

(1) *LEA Detector*. ASY and shockable rhythms were used. The detection thresholds were determined through a greedy search on the two-dimensional feature space to jointly maximize the number of detected ASY and minimize the number of shockable windows incorrectly detected as nonshockable. An additional restriction was imposed: at maximum 5% of shockable windows could be incorrectly classified.

(2) *Sh/NSh Algorithm*. Shockable and ORG windows not detected as NSh by the LEA detector were used to optimize the SVM classifier. To avoid overfitting the SVM to the training set, C and γ were selected using 5-fold crossvalidation [29] to optimize the balanced error rate (BER):

$$\text{BER} = 1 - \frac{1}{2}(\text{TPR} + \text{TNR}), \tag{6}$$

where the true positive rate (TPR) and the true negative rate (TNR) are the capacity of the SVM

Table 1: Number of segments (patients in parenthesis) and characteristics of the CC rate and depth for the training and test datasets. Values for CC rate and depth are presented as median with 5–95 percentiles in parenthesis.

Rhythm type	Training			Testing		
	9-s seg.	Rate (cpm)	Depth (mm)	9-s seg.	Rate (cpm)	Depth (mm)
Shockable	**563 (35)**	**116 (92–143)**	**38 (25–47)**	**622 (34)**	**113 (89–157)**	**35 (20–50)**
Nonshockable	**3132 (110)**	**116 (88–155)**	**36 (20–51)**	**3350 (109)**	**116 (84–159)**	**35 (21–57)**
AS	1173 (66)	118 (92–164)	35 (18–52)	1309 (60)	117 (89–151)	34 (21–52)
ORG	1959 (66)	114 (86–149)	37 (23–51)	2041 (76)	116 (79–164)	35 (21–59)
Total	**3695 (123)**	**116 (89–151)**	**36 (21–51)**	**3972 (124)**	**116 (86–159)**	**35 (21–58)**

classifier to detect shockable and ORG windows, respectively. Weights were assigned to each class to resolve the unbalance in the number of instances per class [28]. The best SVMs using one, two, or three features were compared to the optimal four-feature SVM using McNemar's test.

The performance of the algorithm was measured in the test set in terms of sensitivity and specificity. Since both 3 s windows and 9 s segments correspond to consecutive analyses within a record, the sensitivities, specificities, and their 90% low one-sided confidence intervals (CI) were adjusted for clustering (longitudinal data) within each record, using a longitudinal logistic model fit by generalized estimating equations (GEE) [30, 31]. The analysis was carried out in *R* using the geepack library [32]. Finally, the algorithm was programmed in MATLAB R2013a (Mathworks Inc.) for Windows and processing time performance tests were carried out on a 2.9 GHz Intel i7 with 4 GB of RAM.

3. Results

3.1. Database Description. Our data comprise 7667 9 s segments within 1396 records extracted from 247 OHCA patient episodes. The median number of 9 s segments per record was 3 (1–19, range 1–44). Table 1 shows the number of 9 s segments and the rate and depth of CCs for those segments in the training and test sets. The median CC rate and depth were 116 (88–156) compressions per minute (cpm) and 36 (21–53) mm, respectively.

3.2. Shock Advice Algorithm

3.2.1. Training. Figures 6(a) and 6(b) show the values of P_{LEA} and L_{min} for the ASY and shockable rhythms which presented significant differences between the two groups ($P < 0.001$). The optimal detection thresholds of the LEA detector were

$$P_{\mathrm{LEA}} < 0.44 \quad \text{or} \quad L_{\mathrm{min}} < 0.63. \tag{7}$$

The LEA detector identified as NSh 72.1% of the ASY (true detections) and 0.9% of the shockable (false detections) windows. In addition, 38.8% of the ORG windows were correctly identified as NSh; these rhythms corresponded to very low rate and low electrical activity intervals of ORG rhythms.

Figures 6(c)–6(f) show the values of the features used in the SVM classifier; these values were statistically different for the ORG and shockable rhythms ($P < 0.001$). The SVM based on four features showed a significantly better performance when compared to the SVMs based on the best single, pair, or triplet of features (McNemar's test $\chi^2 > 10$, $P < 0.001$, in all three cases). The optimal working point of the four-feature SVM was ($C = 8.5$, $\gamma = 0.1$), which produced a BER = 0.064, TPR = 0.927, and TNR = 0.944 for the SVM classifier. The receiver operating characteristics analysis on the SVM features resulted in the following area under the curve (AUC) values: 0.948, 0.928, 0.807, and 0.733 for bS, nP, P_{fib}, and P_h, respectively. When combined in the SVM the resulting AUC was 0.971, which reveals the robustness of the classifier.

3.2.2. Test. The optimized SAA was used to classify the 3 s windows in the test set; Table 2 shows a summary of the results. The overall sensitivity and specificity were 89.7% (low one-sided 90% CI, 85.5) and 95.1% (low 90% CI, 94.3), respectively. The 9 s segments were diagnosed using a majority criterion on three consecutive window analyses, this increased the overall sensitivity and specificity to 91.0% (low 90% CI, 86.6) and 96.6% (low 90% CI, 95.9), respectively, and AHA recommendations were met for all rhythm types (see Table 2).

Figure 7 shows two examples (Figures 7(a) and 7(c)) of correctly diagnosed segments and two examples (Figures 7(b) and 7(d)) of incorrectly diagnosed segments. The examples (Figures 7(a) and 7(c)) show that the algorithm works robustly even in the presence of important filtering residuals. However, there were some instances of misdiagnosed segments as shown in Figures 7(b) and 7(d). Errors were generally caused by spiky filtering residuals in shockable rhythms (Figure 7(b)) or large filtering residuals during ASY (Figure 7(d)).

Processing time for the complete algorithm, CPR suppression filter based on the LMS filter followed by the SAA, was on average 8.7 ms per 3 s segment. Processing time was broken down into 5.8 ms for the LMS filter and 2.9 ms for the SAA. For decisions taken by the LEA detector the SAA required only 1.8 ms, and for windows in which the LEA detector and the SVM were used it increased to 4.1 ms. In the worst case scenario processing time for the complete algorithm was under 10 ms.

4. Discussion

This study presents the first attempt to combine two approaches for rhythm analysis during CPR: adaptive filters

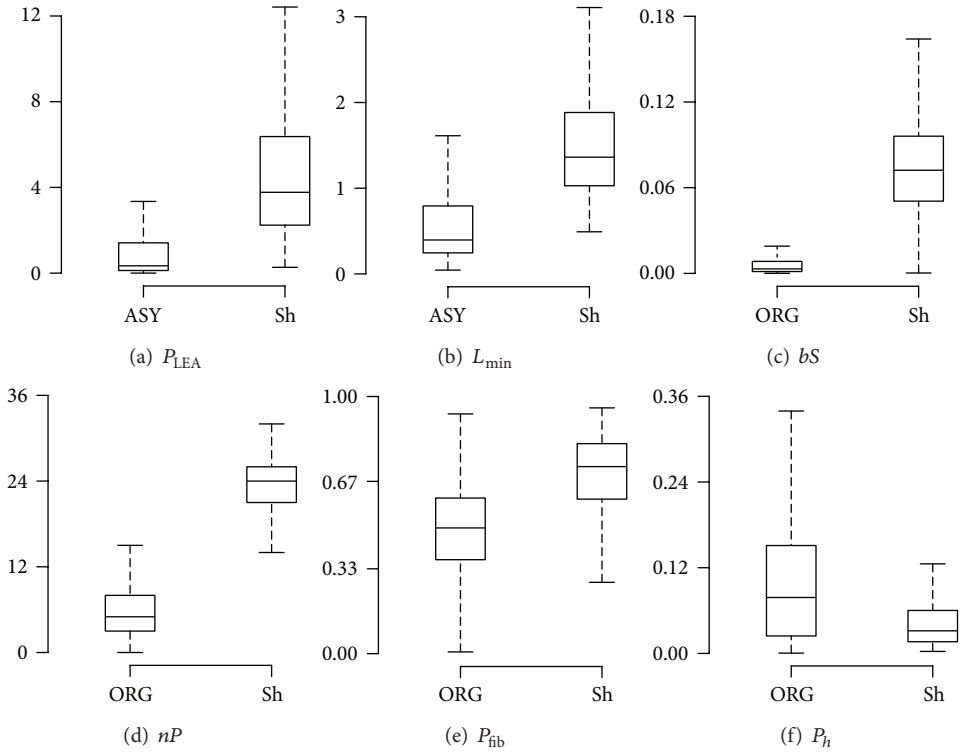


FIGURE 6: Features of the SAA for the rhythm types used in each training stage of the algorithm. For the LEA detector the figure compares ASY versus Sh (panels (a) and (b)), and for the SVM classifier ORG versus Sh (panels (c)–(f)). The boxes show the median and interquartile ranges (IQR) and the whisker shows the last datum within the ±1.5IQR interval. Significant differences were found for the median value of the features between the targeted groups ($P < 0.0001$).

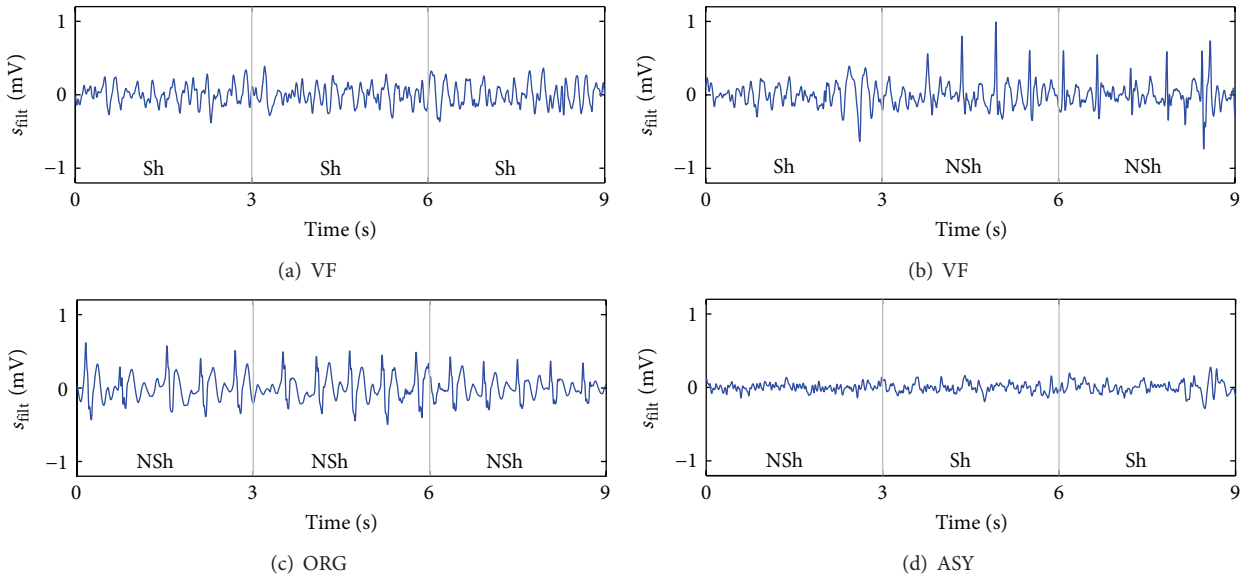


FIGURE 7: Examples of correctly and incorrectly classified 9 s segments. Examples (a, c) are correctly classified despite the presence of large filtering residuals. However, in the VF of panel (b) spiky filtering artifacts cause the erroneous classification. In the ASY of panel (d) filtering residuals are large in the last two windows causing the shock diagnosis.

Table 2: Final classification for the 3-s windows and 9-s segments of the test set compared to the AHA performance goals. Sensitivities, specificities and low one-sided 90% CIs (in parenthesis) were obtained using GEE to adjust for clustering.

Rhythm type	3-s window		9-s segment		AHA goal [18]
	n	Se/Sp	*n*	Se/Sp	
Shockable	**1866**	**89.7 (85.5)**	**622**	**91.0 (86.6)**	>90 (for VF)
Nonshockable	**10050**	**95.1 (94.3)**	**3350**	**96.6 (95.9)**	>95
AS	3927	94.3 (93.1)	1309	96.5 (95.2)	>95
ORG	6123	95.6 (94.6)	2041	96.7 (95.8)	>95

Table 3: Comparative assessment in terms of accuracy and the composition of the databases (% of ASY in nonshockable rhythm in parenthesis) between the method proposed in this study and previous methods tested on OHCA rhythms.

Authors	Method	Accuracy		Testing datasets	
		Se (%)	Sp (%)	Sh	NSh
Eilevstjønn et al. [10]	MC-RAMP	96.7	79.9	92	174 (30%)
Aramendi et al. [19]	LMS filter	95.4	86.3	87	285 (31%)
Tan et al. [20]	ART filter	92.1	90.5	114	4155 (NA)
Li et al. [5]	Direct analysis	93.3	88.6	1256	964 (4%)
Krasteva et al. [6]	Direct analysis	90.1	86.1	172	721 (46%)
Proposed method	Filtering + SAA	91.0	96.6	622	3350 (39%)

to suppress the CPR artifact and an SAA optimized to analyze the rhythm after filtering. Our objective was to increase the specificity, because the low specificity of current methods has restrained their implementation in current defibrillators. Our results indicate that our new design approach might contribute to a substantial increase of the accuracy of rhythm analysis methods during CPR, with results that marginally meet AHA performance goals.

The design efforts were focused on obtaining a high specificity during CPR to allow CCs to continue uninterrupted until the method gives a shock advice. The positive predictive value (PPV) of the algorithm, that is, the confidence in a shock diagnosis, must be kept high to avoid unnecessary CPR interruptions if the underlying rhythm is nonshockable. Since VF is the positive class, the PPV depends on the sensitivity/specificity of the algorithm and on the prevalence of VF, P_{vf}, in the following way:

$$\begin{aligned} \text{PPV}\,(\%) &= 100 \times \frac{\text{TP}}{\text{TP} + \text{FP}} \\ &= 100 \times \frac{\text{Se} \cdot P_{vf}}{\text{Se} \cdot P_{vf} + (1 - \text{Sp}) \cdot (1 - P_{vf})}. \end{aligned} \tag{8}$$

The exact prevalence of VF (reported for the initially observed rhythm as stated in [33]) is unknown and varies among OHCA studies, with figures in the range of 23% to 67% [34, 35]. For the original OHCA studies from which our datasets originated the prevalences of VF were 43% [21] and 41% [22], within the previous range. For the limits of the VF prevalence range, the PPV of our algorithm is high, in the 88.9% to 98.2% range. Furthermore, since the PPV depends on the prevalences, algorithms must be trained to optimize sensitivity/specificity, with emphasis on a large specificity (a specificity of 100% would result in a PPV of 100% regardless of the prevalences).

To this date most methods for rhythm analysis during CPR have focused on the accurate detection of shockable rhythms, resulting in higher values for sensitivity than for specificity. Table 3 compares the accuracy of our method to that of five well-known methods tested on OHCA data that represent the two most successful strategies for rhythm analysis during CPR. Three of those methods are based on adaptive filters [10, 12, 20], and the other two are algorithms designed to directly diagnose the corrupt ECG [5, 6]. Although the sensitivity of our method is up to 4 points below that reported by methods based on adaptive filters, it is still above the value recommended by the AHA, which ensures the detection of a high proportion of shockable rhythms. The higher sensitivity of methods based on adaptive filters may be explained by the fact that filtering residuals are frequently diagnosed as shockable by SAA designed to diagnose artifact-free ECG [14]. In contrast, the 96.6% specificity of our approach is an important improvement with respect to previous approaches in which the specificity was below 91%. We showed that combining the strong points of both approaches may result in an increased accuracy.

The characteristics of the OHCA data used in these studies may affect the sensitivity/specificity results, and in particular the characteristics of CPR, the selection criteria for VF, and the proportion of ASY among nonshockable rhythms. Rate and depth values of CPR in our data are similar to those reported in the original studies [21, 22] and represent the wide range of CPR characteristics found in the field. In particular, the CC rates are high (around 120 cpm), the spectral overlap with OHCA rhythms is therefore large, and suppressing the CPR artifact in our data should be challenging [8]. The CC depth was low even according to the 2000 resuscitation guidelines and lower than the 5 cm recommended in current guidelines [36]. However, no clear

correlation between depth and larger artifacts has been demonstrated to date on human data. Our database only included VF annotated as coarse, as stated in the AHA statement. The three-phase model of cardiac arrest suggests that fine VF occurs when VF transitions from the electric phase into the circulatory or metabolic phases [37]. There is no conclusive evidence that immediate defibrillation is the optimal treatment in these latter phases of VF [38], so from a SAA design perspective it is a sound decision to only include coarse VF. On the other hand, our database has a large proportion of ASY among nonshockable rhythms (39%), in agreement with the fact that ASY is the most frequent nonshockable OHCA rhythm [39]. The high specificity of our method for ASY is particularly important because ASY is the most difficult nonshockable rhythm to detect during CPR [14, 16].

Our study shows that combining adaptive filtering with special SAAs that optimally diagnose the filtered ECG may result in an increased overall accuracy. In addition, the computational cost of the algorithm is low, as shown by the processing time analysis. The SAA algorithm computes at most six ECG features, and implementing our SVM in an AED requires only a few kilobytes of memory for the support vectors and the computation of the discriminant function (see equation (5)). The LMS algorithm using 5 harmonics involves only 10 coefficients [12], which substantially simplifies the filter. In any case, incorporating a CPR artifact filter to current AEDs is more complex than using algorithms that directly analyze the corrupt ECG [5, 6]. Filtering techniques based on the CD signal require the use of external CPR quality devices [40, 41] or modified defibrillation pads [42, 43] to record the acceleration signal. Alternatively other reference signals can be used, such as the thoracic impedance recorded through the defibrillation pads [19]. CPR artifact filters increase the complexity of the software and signal processing units of the AED and may even demand changes in its hardware to acquire reference signals.

Finally, several studies need to be completed before any method could be safely taken to the field. First, more conclusive results require testing the algorithm on data recorded by equipment different from those used for this study and with CPR delivered according to the latest 2010 CPR guidelines. In addition, retrospective studies based on complete resuscitation episodes should be conducted. In this way, the impact of using the method on CPR administration could be evaluated. This involves, among other things, a statistical evaluation of whether the method avoids unnecessary CPR interruptions in nonshockable rhythms and unnecessary CPR prolongations in shockable rhythms [36]. The methodology for such an evaluation has recently been developed [44].

5. Conclusions

This work introduces a new method for rhythm analysis during CPR with a novel design approach aimed at obtaining a high specificity. The method combines an adaptive LMS filter to suppress the CPR artifact with a new shock/no-shock classification method based on the analysis of the filtered ECG. The method resulted in an increased specificity of 96.6% without compromising the sensitivity, with overall performance figures that met AHA requirements.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Research Article

Removal of Cardiopulmonary Resuscitation Artifacts with an Enhanced Adaptive Filtering Method: An Experimental Trial

Yushun Gong,[1] Tao Yu,[2,3] Bihua Chen,[1] Mi He,[1] and Yongqin Li[1,3]

[1] *School of Biomedical Engineering, Third Military Medical University and Chongqing University, 30 Gaotanyan Main Street, Chongqing 400038, China*
[2] *Emergency Department, Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, Guangzhou 510120, China*
[3] *Institute of Cardiopulmonary Cerebral Resuscitation, Sun Yat-Sen University, Guangzhou 510120, China*

Correspondence should be addressed to Yongqin Li; leeoken@gmail.com

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Current automated external defibrillators mandate interruptions of chest compression to avoid the effect of artifacts produced by CPR for reliable rhythm analyses. But even seconds of interruption of chest compression during CPR adversely affects the rate of restoration of spontaneous circulation and survival. Numerous digital signal processing techniques have been developed to remove the artifacts or interpret the corrupted ECG with promising result, but the performance is still inadequate, especially for nonshockable rhythms. In the present study, we suppressed the CPR artifacts with an enhanced adaptive filtering method. The performance of the method was evaluated by comparing the sensitivity and specificity for shockable rhythm detection before and after filtering the CPR corrupted ECG signals. The dataset comprised 283 segments of shockable and 280 segments of nonshockable ECG signals during CPR recorded from 22 adult pigs that experienced prolonged cardiac arrest. For the unfiltered signals, the sensitivity and specificity were 99.3% and 46.8%, respectively. After filtering, a sensitivity of 93.3% and a specificity of 96.0% were achieved. This animal trial demonstrated that the enhanced adaptive filtering method could significantly improve the detection of nonshockable rhythms without compromising the ability to detect a shockable rhythm during uninterrupted CPR.

1. Introduction

Early defibrillation is critical for the survival of patient who suffered from cardiac arrest [1, 2]. However, the application of high quality of cardiopulmonary resuscitation (CPR) introduces strong artifact components into the electrocardiogram (ECG) signal, which reduces the accuracy of the shock/nonshock decision of automated external defibrillators (AEDs) [3]. Thus, chest compressions (CC) are mandated to be interrupted in the current AEDs in order to perform a reliable rhythm analysis and provide appropriate defibrillation prompt to the rescuers. But even seconds of interruptions of CC adversely affects the rate of restoration of spontaneous circulation (ROSC) and survival [4]. According to an experimental study, the likelihood of successful resuscitation decreased as much as 50% with a 20-second interruption of CC [5]. Actually, clinical studies have also confirmed that longer pauses in CC before and after defibrillator shocks were independently associated with a decrease in survival to hospital discharge [6, 7]. When the hands-off intervals were minimized, significantly better outcomes were achieved and reported [8, 9]. Therefore, the latest guidelines from the American Heart Association (AHA) and the European Resuscitation Council (ERC) recommended minimizing these hands-off intervals between compression and shock [10, 11].

If accurate cardiac rhythm analysis can be performed during CPR, these interruptions will be minimized or totally avoided. During the last decade, numerous digital signal processing techniques have been developed to remove the artifacts or interpret CC corrupted ECG during CPR. Sensitivity and specificity are the proportion of correctly identified shockable and nonshockable rhythms, respectively, and are used to evaluate the performance of artifact suppression method. Algorithms removing artifacts using only the ECG signal, including independent component analysis (ICA) [12] and coherent line removal algorithm [13], have improved the

sensitivity to 99.8% and the specificity to 83.2% for detecting a shockable rhythm. Methods filtering the CPR artifact using additional references, such as Gabor multipliers [14], Kalman filter [15], adaptive filter [16–19], and multichannel recursive adaptive matching pursuit (MC-RAMP) filter [20], have improved the sensitivity and specificity to 95.6% and 90.5%. To identify a shockable rhythm during CPR, Li et al. [21] searched the identifiable components directly in the corrupted ECG signal using morphology consistence evaluation. A sensitivity of 93.3% and specificity of 88.6% were reported in a dataset which consisted of 229 victims during out-of-hospital cardiac arrest. Although the sensitivity for detecting a shockable rhythm was significantly improved with the application of these techniques, the specificity was still below the 95% limit recommended by the AHA task force on AEDs for accurately detecting nonshockable rhythms [22]. Further studies are, therefore, still required to analyze the interaction between the artifact and underlying rhythms and to improve the accuracy of nonshockable rhythm decision [23, 24].

In the present study, the effects of CC on signal-to-noise ratio (SNR) at different types of underlying rhythms (ventricular fibrillation (VF), pulseless electrical activity (PEA), and asystole (ASY)) were firstly analyzed in an adult porcine model of prolonged cardiac arrest and CPR. An enhanced adaptive filtering method was then developed to suppress the CPR artifact and evaluated by comparing the sensitivity and specificity for shockable rhythm detection before and after filtering.

2. Materials and Methods

2.1. Experiment Procedure and Data Collection. The experimental data were collected from 22 male adult pigs that experienced prolonged cardiac arrest and CPR. The porcine model has been well established to simulate real out-of-hospital scenarios due to the fact that heart size, blood pressure, and heart rate are similar to those in humans [25]. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg) and was completed by ear vein injection of sodium pentobarbital (30 mg/kg). VF was electrically induced by applying a 5 mA alternate current through a pacing catheter in the right ventricle. CPR, including CC and ventilation, was begun after 6 minutes of untreated VF (Group A) in 14 animals [26]. The compression depth (CD) was randomized to either 25% or 17% of the anterior posterior diameter of the chest during the first 4 minutes of CPR and 20–25% after 4 minutes. In another 8 animals with the same weight and chest size, CPR was begun after 11 minutes of untreated VF (Group B). CD was comparable to 20–25% of the anterior posterior diameter of the chest. For all of the animals, manual CC were performed by two experienced emergency medical doctors at a rate above 100 per minute. The animals were manually ventilated with a bag-valve device during CPR. CC were synchronized to provide a compression/ventilation ratio of 30 : 2 with equal compression-relaxation intervals. After 2 minutes of CC in Group A and 6 minutes of compression in Group B, a defibrillation was attempted with a single 120 J rectilinear biphasic shock. One dose of epinephrine (30 $\mu g \cdot kg^{-1}$) was given through the right atrial catheter after 2 minutes of CPR in Group B. CC were immediately resumed followed by ECG rhythm analysis within 5 seconds until confirmation of spontaneous circulation. If spontaneous circulation was not restored, CC were continued for another 2 minutes, after which defibrillation was attempted with another single 120 J shock. This sequence was repeated for a maximum of 5 cycles.

The ECG, acceleration, and transthoracic impedance (TTI) waveform were continuously measured and recorded through a data acquisition system supported by Windaq hardware/software (Dataq Instruments Inc., Akron, OH, USA) at a sample rate of 300 Hz. During CC, the acceleration and TTI signals also served as feedback to control the compression rate and depth. The ECG was measured from the output of a commercial defibrillator (M-Series, Zoll medical corporation, Chelmsford, MA, USA) with the use of a hard gel type of adult defibrillation/pacing pads (stat-padz, Zoll Medical Corporation, Chelmsford, MA, USA) that were applied with an anterior to lateral placement. TTI waveform was recorded through a user designed circuit which was parallelly connected with the defibrillator using a sinusoid-wave excitation current of 2 mA and 30 kHz across the defibrillation pads. The acceleration signal was recorded from an accelerometer-based handheld CPR device (CPR-D-padz, Zoll Medical Corporation, Chelmsford, MA, USA) that was placed on the surface of the animal's chest just above the heart and underneath the rescuer's hands during CC.

Data were analyzed offline through user designed software using Matlab (The MathWorks, Inc., Natick, MA, USA). ECG, together with acceleration and TTI signals during CPR, was extracted and annotated from the digitalized experimental records. The CD was calculated from the double integration of acceleration signal. Each segment consisted of 4-second corrupted signal and 3-second artifact-free signal, either during ventilation or during rhythm analysis. These segments were then annotated as VF, PEA, or ASY by an experienced emergency medical doctor. As shown in Figure 1, a disordered electrical activity without the presence of observational QRS and with the peak-to-peak voltage greater than 0.1 mV was annotated as VF. The presence of at least one QRS complex in a segment was classified as PEA. A segment with peak-to-peak voltage less than 0.1 mV was annotated as ASY. Segments with rhythm transitions or defibrillation were excluded from the dataset.

2.2. Estimation of SNR. To investigate the effects of CC on SNRo (before filtering) at different types of underlying rhythms (VF, PEA, and ASY) and performance of the proposed filtering method, we estimate the SNRo and the SNRf (after filtering) of the CPR corrupted ECG based on the contiguous artifact-free signal [27]. Assuming that the underlying ECG and CPR artifact are uncorrelated, the power of CPR artifact can be obtained through subtracting the power of corrupted ECG by the power of clean ECG. Figure 2 shows the examples of signal selection for SNRo estimation in each segment. A 3-second corrupted ECG signal and another

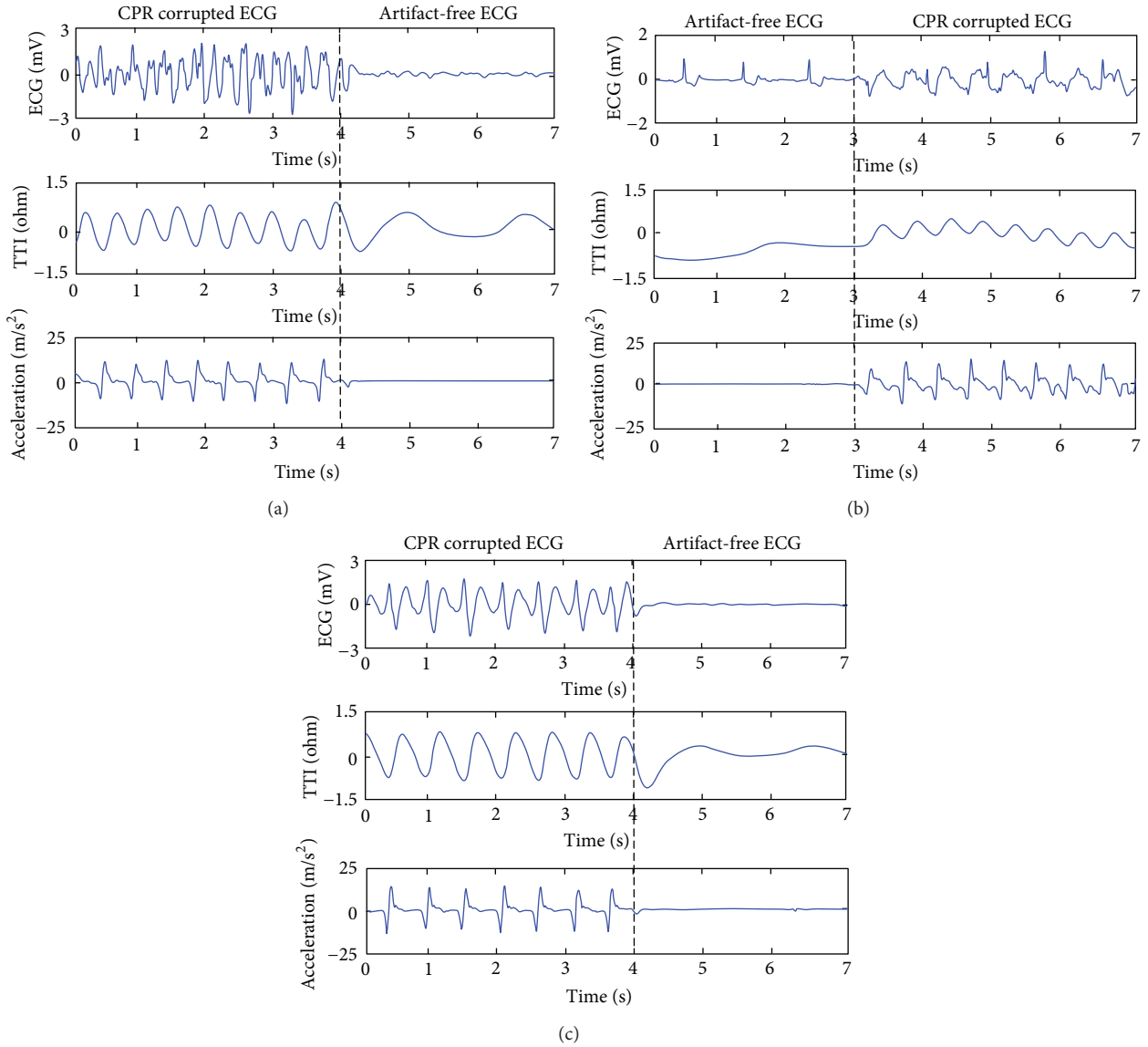

Figure 1: Segments of ECG and reference signals during cardiopulmonary resuscitation (CPR). (a) Ventricular fibrillation with and without chest compression (CC). (b) Pulseless electrical activity (PEA) without and with CC. (c) Asystole (ASY) with and without CC. TTI: transthoracic impedance.

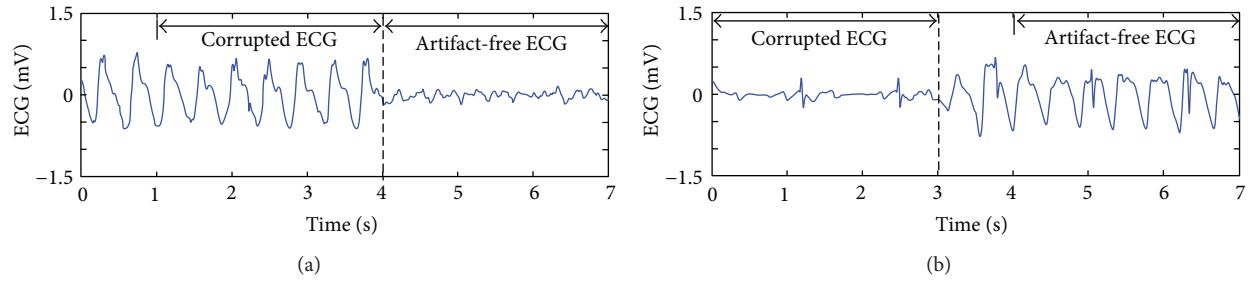

Figure 2: Examples of signal selection for SNR estimation. The CPR corrupted signal was selected either from the latest 3 seconds of chest compression (CC) (a) or 1 second after the beginning of CC (b).

3-second artifact-free signal are used to calculate the SNRo with the following equation:

$$\mathrm{SNR} = 10 \cdot \log_{10}\left(\frac{\sigma_s^2}{\sigma_x^2 - \sigma_s^2}\right), \quad (1)$$

where σ_s^2 is the variance of underlying ECG signal and σ_x^2 is the variance of corrupted ECG signal. The SNRf is also estimated with (1), except that the variance of underlying ECG is calculated by the filtered uncorrupted 3-second signal, and the variance of artifact is calculated by the subtraction of the variance of underlying ECG and the variance of filtered corrupted ECG signal.

The estimation is based on the hypothesis that time-limited VF and ASY can be considered quasi-stationary signal. On the other hand, since the energy of a normal sinus rhythm depends on the number of QRS complexes appearing within a segment, we therefore exclude the segments that have unequal numbers of QRS complex within the selected artifact-free and corrupted ECG signals when the underlying rhythm is annotated as PEA.

2.3. The Enhanced Adaptive Filtering Method. To suppress the CC related artifacts (CC-artifact), an enhanced adaptive filtering method is developed by estimating the proportion of artifact within the CPR corrupted ECG signal. The flowchart of the proposed method is shown in Figure 3.

The corrupted ECG and reference (TTI) signals are firstly preprocessed by a 4th order Butterworth band-pass filter (0.2–45 Hz) to remove offset and high frequency noise. The power spectral density (PSD) of reference and preprocessed ECG signals are then calculated through dividing the square of the amplitude of fast Fourier transform (FFT) by the length of data points. The frequency of CC f_{CC} is obtained by the PSD of TTI:

$$f_{\mathrm{CC}} = \arg\max_f P_{\mathrm{TTI}}(f). \quad (2)$$

The power of artifact is computed through the PSD of corrupted ECG with the use of f_{CC} and its harmonics. The proportion of the artifact power pro is calculated by

$$\mathrm{pro} = \frac{\sum_{k=1}^{N} P_S(k \cdot f_{\mathrm{CC}})}{\sum_{f=0}^{f_s/2} P_S(f)}, \quad (3)$$

where k is the order of harmonics ($N = 3$) and f_s is the sampling rate.

The proportion of the artifact power is then compared with a predefined threshold. If the proportion pro is greater than the preset threshold, the adaptive filter will be applied to the ECG signal to suppress the CPR artifact.

In this enhanced adaptive filtering method, normalized least mean squares (NLMS) is used to adjust the coefficient matrix of adaptive filter, and the step size is dynamically adjusted by the estimated artifact proportion pro:

$$W(n) = W(n-1) + \frac{\mu \cdot \mathrm{pro}}{\|X\|^2} \cdot X(n-1) \cdot e(n). \quad (4)$$

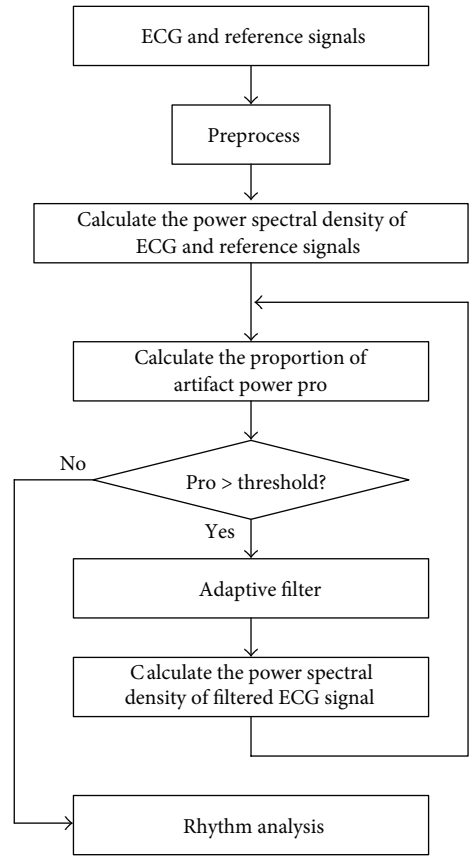

Figure 3: Flowchart of the enhanced adaptive filtering method.

The step size μ is limited by the norm of reference signal $\|X\|$ and proportion of artifact pro. The coefficient matrix $W(n)$ at state n is decided by the previous state $W(n-1)$, the reference signal TTI $X(n-1)$, and the estimated ECG signal $e(n)$:

$$e(n) = s_{\mathrm{in}}(n) - W(n) X(n), \quad (5)$$

where $s_{\mathrm{in}}(n)$ is the input corrupted ECG signal and $W(n)X(n)$ is the estimated CPR artifact.

After filtering, the proportion of artifact pro of the filtered signal is recalculated to assess the SNRf level. If pro is still greater than the preset threshold, another iteration of filtering process will be applied to the filtered signal with updated step size. Otherwise, the filtered ECG signal will be outputted for rhythm analysis. In this study, the length of the coefficient $W(n)$ is 21, and the step size μ is 0.15.

In order to compare the performance with the traditional fixed coefficient high-pass filter [28], a 4th order Butterworth high-pass filter is performed to the corrupted ECG signal to suppress the CPR artifact. Since the average compression rate is 2.11 Hz in this study, the cutoff frequency is 6.5 Hz to remove the first 3 harmonics of the artifact.

2.4. Rhythm Classification Algorithm. To evaluate the performance of the proposed method, the sensitivity and specificity for detecting a shockable rhythm before and after filtering

Table 1: Estimated signal-to-noise ratio (SNR) for pulseless electrical activity (PEA), ventricular fibrillation (VF), and asystole (ASY) before and after filtering.

	Unfiltered	Adaptive filter	High-pass filter
Medians (dB) (25/75 percentiles)			
VF	−9.3 (−14.9/−3.6)$^{\triangle\triangle}$	0.2 (−5.1/4.5)**	0.1 (−4.2/0.9)**
PEA	−6.2 (−9.0/−1.12)$^{\triangle\triangle}$	0.1 (−3.6/3.4)**	−2.0 (−7.4/−0.6)**
ASY	−21.2 (−24.2/−18.5)$^{\triangle\triangle}$	−12.7 (−15.0/−4.4)**	−7.1 (−10.7/−6.3)**
Range (dB) (min./max.)			
VF	−26.1/9.6	−18.2/20.0	−19.7/20.4
PEA	−16.0/9.9	−7.6/19.9	−14.0/14.7
ASY	−31.6/−10.0	−20.6/2.4	−18.4/1.7

**Compared with unfiltered signal, $P < 0.001$; $^{\triangle\triangle}$comparison among rhythm types, $P < 0.001$.

are compared with an established rhythm classification algorithm named phase space reconstruction (RSR) [29, 30]. This specific algorithm is selected because it can provide accurate rhythm classification within a relative short time window. In this method, signal $s(t)$ is plotted on x-axis and $s(t+\tau)$ with a delay time of τ is plotted on y-axis to form a two-dimensional phase space diagram. A 40×40 grid is produced and the number of boxes visited by the signal is counted. Ratio r' is calculated through dividing the area that is filled with signal curve B_v by the total area of the diagram B_a. In the current study, the maximum number of data points visited in the box $C_{\max}$ is used to modify the ratio r' which is used to classify PEA and VF:

$$r' = \frac{B_v}{B_a} + \frac{1}{C_{\max}}. \tag{6}$$

The average peak-to-peak amplitude of the filtered signal A' is used to detect ASY. The 3- second ECG signal is split into 3 rectangular nonoverlapping windows. And the difference between maximum and minimum of the signal in each window is calculated and the average of these differences is represented as the value of A'.

A 3-second rectangular window is used to perform PSR, and the value of τ is 0.5 seconds. The threshold of the amplitude A' and the ratio r' are optimized with the artifact-free ECG signals to produce the optimum sensitivity/specificity values. The classification criteria are presented as

$$\begin{aligned} &A' \le 0.1\,\text{mV} && \text{ASY} \\ &A' > 0.1\,\text{mV}, \quad r' \le 0.24 && \text{PEA} \\ &A' > 0.1\,\text{mV}, \quad r' > 0.24 && \text{VF}. \end{aligned} \tag{7}$$

2.5. Statistical Presentation. The distributions of SNRo of the CPR corrupted ECG signal did not pass the Kolmogorov-Smirnov normality test and were presented as medians (25/75 percentile). The Wilcoxon rank sum test was used for median values comparison. The relationship between SNRo and CD was tested with Pearson correlation coefficients.

The performance of the filtering method was expressed as sensitivity and specificity. Sensitivity and specificity of ECG signals before and after filtering were compared with the classification results of artifact-free ECG signals using Chi-square test. A P value of 0.01 was considered significant.

3. Results

The average duration of CPR was 6.8 ± 3.2 minutes. A total of 624 segments were extracted and 61 segments were excluded according to the exclusion criteria. Finally, a total of 563 CC related segments, including 283 VF, 208 PEA, and 72 ASY, were obtained for the study. The amplitude of artifact-free ECG signals was 0.7 ± 0.6 mV for VF, 0.8 ± 0.6 mV for PEA, and 0.05 ± 0.04 mV for ASY. The amplitude of corrupted ECG signals was 2.1 ± 1.2 mV for VF, 1.9 ± 0.8 mV for PEA, and 1.0 ± 0.7 mV for ASY.

3.1. Relationship between CC and SNR. A total of 107 segments of PEA were used for SNR estimation because the numbers of QRS complex within the selected artifact-free and corrupted ECG signals were equal. Table 1 shows the medians (25/75 percentiles) and minimum and maximum value of the estimated SNR based on annotated underlying rhythms. A relative lower SNRo was observed for VF compared with that of PEA ($P < 0.001$) and the SNRo of ASY was significantly lower than PEA and VF ($P < 0.001$). After filtering with the proposed method and high-pass filter, the SNRfs were greatly improved in all of the rhythms ($P < 0.001$).

The linear regression result between SNRo and CD is shown in Figure 4. The SNRo of the full database was negatively correlated with the CD ($r = -0.227$, $P < 0.001$). When each of the rhythms was investigated individually, negative correlation between CD and SNRo was only observed in VF ($r = -0.239$ and $P < 0.001$).

3.2. Performance of the Enhanced Adaptive Filtering Method. Table 2 shows the rhythm classification results for the artifact-free, CPR corrupted, and filtered signals with the use of PSR. The sensitivity and specificity were 99.0% and 98.2% for artifact-free signal. However, the specificity decreased to 46.8% and the sensitivity increased to 99.3% when the ECG signals were corrupted by CPR. After filtering by enhanced adaptive filter and high-pass filter, a sensitivity of 93.3% and 93.0% and a specificity of 96.0% and 80.4% were achieved.

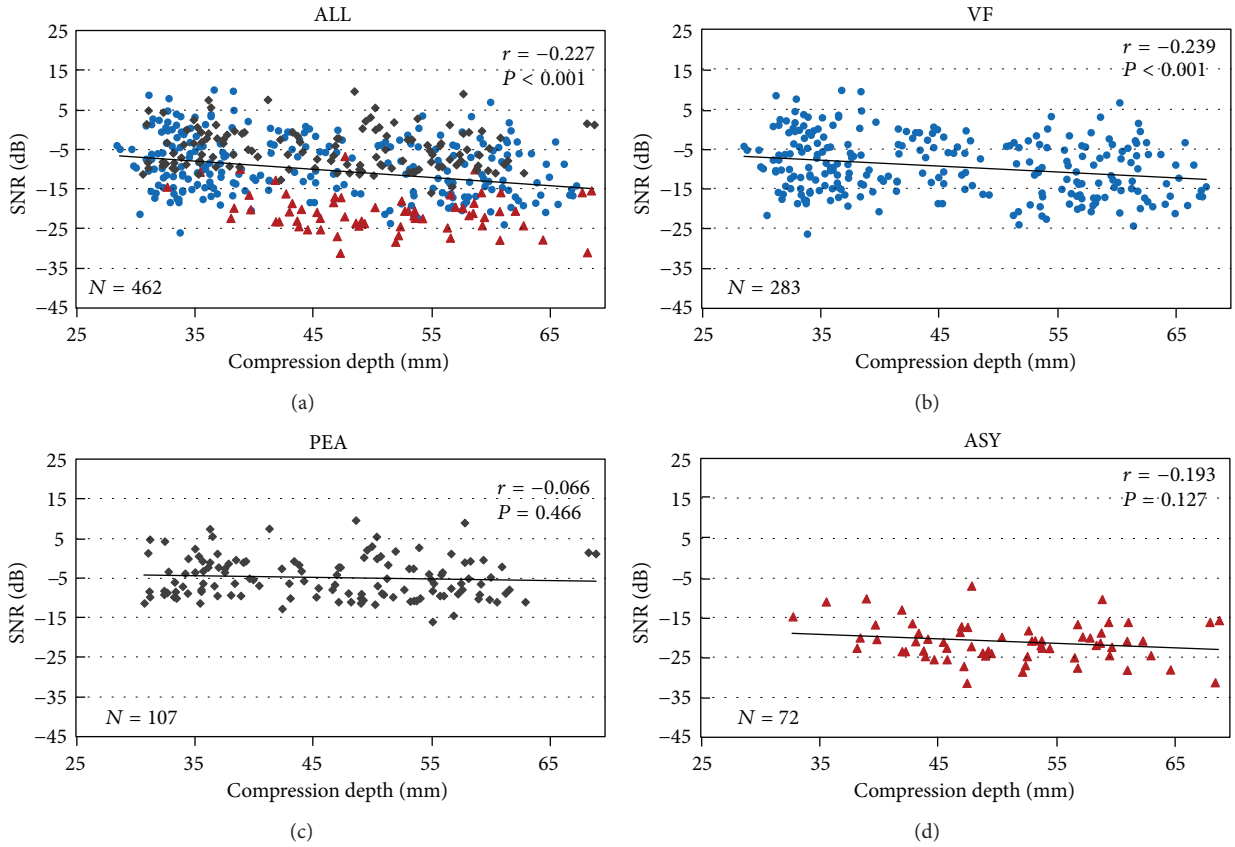

Figure 4: Linear regression results between SNRo and CD for the full database and different types of underlying rhythms (ventricular fibrillation, VF; pulseless electric activity, PEA; asystole, ASY).

Table 2: Sensitivity and specificity for the artifact-free ECG and CC corrupted signals before and after filtering.

	Rhythm	Number	Artifact-free	Unfiltered	Adaptive	High-pass
Shockable (sensitivity)	VF	283	99.0%	99.3%	93.3%**	93.0%**
Nonshockable (specificity)	All	280	98.2%**	46.8%	96.0%**##	80.4%**
	PEA	208	98.6%**	53.9%	97.6%**##	86.3%**
	ASY	72	97.2%**	26.4%	91.7%**##	63.9%**

**Compared with unfiltered signals, $P < 0.001$ and ##compared with high-pass filter, $P < 0.001$. VF: ventricular fibrillation, PEA: pulseless electrical activity, and ASY: asystole.

4. Discussion

The present study confirmed that the SNRo of CPR corrupted ECG was negatively correlated with CD in a porcine model of prolonged cardiac arrest and CPR. Based on this observation, we developed an enhanced adaptive filtering method to suppress the CC-artifact by estimating the proportion of artifact within the corrupted ECG signal. The experimental results demonstrated that the enhanced adaptive filtering method could effectively reduce the residual component of artifact and improve the SNR of the ECG signal as well as the outcome of specificity.

4.1. Relationship between CC and SNR. The CC-artifact was predominant from the electrode-skin interface and generated by the contraction of thoracic muscles with direct impact of the compressions on chest wall [31]. Therefore, it was anticipated that deeper compression would cause more chest movements and introduced severe artifact to the ECG. In this animal study, we demonstrated that the SNRo of CPR corrupted ECG signals was negatively related to CD. However, when each of the rhythm was investigated, the SNRo was significantly lower for ASY compared to PEA and VF and the negative correlation between CD and SNRo was only observed in VF. For VF, the signal energy homogeneously distributed among all VF segments, and the value of SNRo was therefore correlated with the value of CD. For PEA, the energy of underlying signal depended on the number of QRS complexes appearing within a segment and might impact the correlation between SNRo and CD. For ASY, the energy of underlying signal is theoretically nearly 0 so that the SNRo should be $-\infty$. However, randomized noisy signal

and power supply artifact, together with artifacts produced by the amplifier and A/D converter, were introduced during measurement. Even though a band-pass filter was applied before analysis, the irregular residual signals within underlying ASY might still affect the value of signal energy and lead to insignificant correlation between SNRo and CD.

Compared with the result that was reported by de Gauna et al. [27], a relatively lower SNRo was observed in our study. The inconsistence may relate to the increased CD recommendation of the latest guidelines, which require a minimum of 50 mm in CD to ensure high quality CPR [10, 32]. At the same time, signal characteristics of porcine ECG such as amplitude and frequency might be different from that of human. The resulted SNRo thus would be affected by the spectral energy calculated from signal amplitude and frequency.

4.2. Improved Performance for the Enhanced Adaptive Filtering Method. Based on the findings that SNRo was negatively correlated with CD, we developed an enhanced adaptive filtering method to suppress the CPR artifact by estimating the proportion of artifact with the use of TTI as reference. Compared with the corrupted signal, both traditional fixed coefficient high-pass filter and proposed method could greatly improve the SNR and specificity. But compared with a specificity of 80.4% for high-pass filter, a remarkable improvement was achieved for the proposed method with a value of 96.0%.

The following modification in removing the CPR related artifact might contribute to the improved performance of the proposed method. Firstly, a parameter was introduced to estimate the proportion of artifact from PSD of ECG signal with the use of compression frequency as reference. The proportion of artifact was correlated with the power of artifact and therefore the SNR level. Secondly, the step size of commonly used LMS adaptive filter was dynamically adjusted by referenced TTI signal and the estimated proportion of artifact. This modification provided greater stability and convergence speed compared with traditional LMS based adaptive method which was used by Irusta et al. [17] and Aramendi et al. [18]. Therefore, the specificity of the proposed method was greatly improved compared with their results even though similar reference signals were used in both studies. Thirdly, the proportion of artifact was also used as an indicator to assess the artifact level in the filtered signal and to control the filtering iteration. This process was terminated only if the artifact level decreased to a predefined threshold. Compared with the MC-RAMP method which took use of several kinds of reference signals proposed by Husøy et al. [33] and Eilevstjønn et al. [20], the residual component of artifact could be further suppressed and the reliability for detecting a nonshockable rhythm was markedly improved.

Besides the enhanced adaptive filter, the algorithm used for rhythm classification also contributed to the improved specificity. The parameters were optimized according to clean ECG signals recorded from the animals when SPR was used [29]. Firstly, the ratio r' was adjusted by the maximum number of data points visited in the box. This adjustment enlarged the difference between VF and PEA. Secondly, both window size and delay time were optimized when the phase space diagram was reconstructed. Consequently, the threshold of r' increased from 0.15 to 0.24 for the detection of VF.

Although the SNR and specificity were greatly improved after filtering, the sensitivity decreased from 99.3% to 93.3%. It is because the enhanced filtering method also suppressed the component of underlying ECG signals while removing the CPR related artifact. As a result, amplitude of fine VF might be reduced to a level that is below the criteria for classification. When the nonshockable rhythms were investigated separately, the specificity for detecting ASY was relatively lower compared with that of PEA and still below the 95% limit recommended by AHA task force on AEDs [22]. This was consistent with the observation that CPR artifact suppression was particularly difficult in ASY [34, 35]. Yet, the 91.7% specificity for detecting ASY was still superior to reported results and the adverse effects of interruption of CC are likely to override the decrease in correctly detecting ASY.

4.3. Limitations. There are limitations that need to be acknowledged and addressed regarding the present study. Firstly, although the SNRo of CPR corrupted ECG was demonstrated to be negatively correlated with CD for the full database, this correlation was only observed in VF when different ECG rhythms were investigated individually. Additionally, the anatomy structure of human chest was different with that of the animals. Therefore the relationship between artifact level and CD in human beings at different underlying rhythms is still needed to be investigated. Secondly, only TTI signal was used as reference in this study; the effects of different reference signals on the performance of the proposed method have not been investigated. Thirdly, although a great improvement in specificity was achieved in this experimental trial, characteristics of ECG waveform, together with the CPR related artifact, may differ from the data that are recorded from patients who experienced out-of-hospital cardiac arrest and CPR. Performance of the proposed method therefore needs further clinical validating studies. Finally, even though the specificity for detecting a nonshockable rhythm was greatly improved and above the 95% limit recommended by the AHA task force on AEDs [22], the accuracy for detecting ASY was still low. Further studies that focused on the suppressing artifact of ASY, as well as the classification between ASY and VF, still need to be conducted.

5. Conclusion

This experimental animal trial demonstrated that the SNRo of ECG signal corrupted by CPR artifact was negatively correlated with CD and the enhanced adaptive filtering method could significantly improve the detection of nonshockable rhythms without compromising the ability to detect a shockable rhythm during uninterrupted CPR.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Review Article

Oxygenation, Ventilation, and Airway Management in Out-of-Hospital Cardiac Arrest: A Review

Tomas Henlin,[1] Pavel Michalek,[2] Tomas Tyll,[1] John D. Hinds,[3] and Milos Dobias[2]

[1] *Department of Anaesthesia and Intensive Medicine, Military University Hospital, 1st Medical Faculty, Charles University in Prague, 160 00 Prague, Czech Republic*
[2] *Department of Anaesthesia and Intensive Medicine, General University Hospital, 1st Medical Faculty, Charles University in Prague, 120 21 Prague, Czech Republic*
[3] *Department of Anaesthesia, Craigavon Area Hospital, BT63 5QQ Portadown, Northern Ireland, UK*

Correspondence should be addressed to Pavel Michalek; pafkamich@yahoo.co.uk

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Recently published evidence has challenged some protocols related to oxygenation, ventilation, and airway management for out-of-hospital cardiac arrest. Interrupting chest compressions to attempt airway intervention in the early stages of OHCA in adults may worsen patient outcomes. The change of BLS algorithms from ABC to CAB was recommended by the AHA in 2010. Passive insufflation of oxygen into a patent airway may provide oxygenation in the early stages of cardiac arrest. Various alternatives to tracheal intubation or bag-mask ventilation have been trialled for prehospital airway management. Simple methods of airway management are associated with similar outcomes as tracheal intubation in patients with OHCA. The insertion of a laryngeal mask airway is probably associated with worse neurologically intact survival rates in comparison with other methods of airway management. Hyperoxemia following OHCA may have a deleterious effect on the neurological recovery of patients. Extracorporeal oxygenation techniques have been utilized by specialized centers, though their use in OHCA remains controversial. Chest hyperinflation and positive airway pressure may have a negative impact on hemodynamics during resuscitation and should be avoided. Dyscarbia in the postresuscitation period is relatively common, mainly in association with therapeutic hypothermia, and may worsen neurological outcome.

1. Introduction

Since the late 1950s, when Safar et al. described the ABC principle in cardiopulmonary resuscitation [1, 2], the letters "A" (airway) and "B" (breathing, ventilation) have been the cornerstones of resuscitation in cardiac arrest. For many years, this algorithm remained unchanged. Opening the airway, delivering oxygen at 100% concentration, insertion of a tracheal tube, and application of intermittent positive pressure ventilation (IPPV) were considered "gold standards" in oxygenation and airway management. This applied both during cardiopulmonary resuscitation for cardiac arrest in adults and also in the early period after restoration of spontaneous circulation (ROSC). However, the outcomes of patients after out-of-hospital cardiac arrest (OHCA) remained quite poor. In the United States, survival rate to hospital admission is 26.3%, and only 9.6% of patients are able to be discharged from inpatient care [3].

Many CPR standards have been challenged during the last decade in adult cardiac arrest of nontraumatic origin. This has included the method of delivering oxygen, its ideal fraction, ventilation strategies, timing, and utilizing adjuncts other than a tracheal tube for maintenance of airway patency.

2. Management during Resuscitation

2.1. Oxygenation in Cardiac Arrest. Oxygen requirements in cardiac arrest and in the period after return of spontaneous circulation (ROSC) have been extensively studied during recent years. Maximizing oxygen delivery (DO_2) is paramount during the period of cardiac arrest and ineffective

circulation for aerobic metabolism and synthesis of adenosine triphosphate (ATP) [4, 5]. High paO_2 does not cause intracellular or tissue hyperoxia at this time. The consensus is that, during cardiac arrest, 100% oxygen should be delivered to victims in order to increase arterial and tissue pO_2 [6, 7]. Debate continues as to whether oxygen should be delivered via bag-mask ventilation, tracheal tube, supraglottic airway devices or via passive oxygenation [8, 9]. What is more controversial is the most appropriate oxygen fraction (FiO_2) to deliver once restoration of spontaneous circulation has been achieved [10]. Oxygenation strategies in the post-ROSC period are described in detail in another section of this paper.

Novel and alternative oxygenation methods and strategies in adult out-of-hospital cardiac arrest are discussed in following paragraphs.

2.2. Concept of Passive Oxygenation. The concept of continuous passive flow of oxygen to the airway was developed on animal models (dogs) in 1982 [11]. Same authors showed that anesthetized and paralyzed dogs may be oxygenated using this method for a relatively long period [12]. Passive oxygenation was first described in humans in 1991 [13]. Brochard and colleagues used specially equipped tracheal tubes with inserted microcannulas which allowed delivery of a constant flow of concentrated oxygen in ICU patients during disconnections of their breathing circuit. This study was followed by Saïssy et al. who evaluated passive insufflation of oxygen in adult patients during cardiac arrest outside the healthcare facilities [14]. The design of this study was prospective, randomized, and controlled. In total, 48 persons were managed using passive oxygenation, while, in the control group, another 47 patients were ventilated with intermittent positive pressure ventilation. There were no differences in the main outcomes studied—percentage of patients with ROSC or number of victims surviving until hospital admission.

Unfortunately, the neurological outcome of resuscitated individuals was not reported. A subsequent large prospective randomized trial evaluated 1,042 patients with OHCA, assigned to receive either conventional mechanical ventilation or constant flow insufflation of oxygen (CFIO) [15]. The authors did not find any difference in ROSC rates, admissions to hospital, or successful discharge from intensive care facilities. The ICU discharge rate was very low in both groups (2.3% conventional ventilation versus 2.4% in CFIO patients). These two studies used passive oxygen insufflation through a modified tracheal tube (Boussignac tube).

Different results were reported by a group from Arizona. In their first study, Bobrow et al. retrospectively analyzed 1,019 patients who were managed during resuscitation either with positive pressure bag-mask ventilation or with passive insufflation of oxygen through an oropharyngeal airway [16]. Significantly higher survival without neurological deficit was found in the passive oxygen insufflation subgroup—38.2% versus 25.8%, though only in witnessed VF/VT arrest. No difference in outcomes was noted in this study for unwitnessed VF/VT arrest patients or for cardiac arrests caused by nonshockable rhythms. The same group of researchers evaluated in total 4415 scenarios of OHCA in adults caused by a heart disease during a 5-year period [17]. Persons in this study were found by lay bystanders. They were divided into three groups according to the mode of CPR—conventional CPR with chest compressions and mouth-to-mouth breathing, chest compression-only CPR (COCPR), and no CPR provided on scene. COCPR group had the highest survival to discharge from hospital—13.3%. While the results of previous studies suggested a beneficial role of passive oxygen insufflation, the latest trial of Bobrow et al. [17] and results of other studies [18] suggested that the main advantage of this mode of resuscitation—COCPR or cardiocerebral resuscitation (CCR)—is probably through the constant delivery of chest compressions, without interruptions for advanced airway interventions, than the passive application of oxygen "per se." Therefore, cardiocerebral resuscitation is accepted in the early phases of OHCA of cardiac origin [19]. Several animal studies have reported the usefulness of CFIO in the early stages of cardiac arrest compared with conventional ventilation, but their interpolation into human medicine is problematic [20, 21]. Passive insufflation of oxygen is probably not sufficient for an adequate gas exchange during advanced stages of cardiac arrest when chest resistance is higher and lung compliance significantly decreases [22].

Both ERC and AHA guidelines mention passive oxygen delivery in their recent guidelines [6, 7] but do not recommend its routine use during cardiopulmonary resuscitation until more clinical data become available.

2.3. Airway Management Strategies. Management of the patent airway during OHCA may be divided into basic and advanced. Basic airway management consists of the manual relieving of upper airway obstruction ("triple maneuver"), bag-valve mask ventilation (BMV), or the insertion of oropharyngeal or nasopharyngeal airway [6, 7]. Techniques of advanced airway management include the insertion of a supraglottic airway device (SAD) [23], tracheal intubation [24], insertion of Combitube [25], or cricothyrotomy [26]. For many years, all resuscitation algorithms and protocols recommended early tracheal intubation as a part of prehospital advanced life support (ALS). Arguments favoring early tracheal intubation mainly revolved around expectations for better control of the airway, protection against upper airway obstruction, decreased risk for aspiration of gastric contents, and better control of carbon dioxide removal [25]. The strategy of airway management in OHCA in adult patients has gradually shifted towards less invasive techniques during the last decade. ERC guidelines from 2010 recommend performing prehospital tracheal intubation only if a competent intubator is present at the site of OHCA, and with only minimal interruption of chest compressions [6, 8]. AHA guidelines recommend using the most familiar device for the rescuer and conclude that an insertion of supraglottic airway device may be an equivalent to bag-mask ventilation or tracheal intubation [7].

2.3.1. Tracheal Intubation. The major concerns associated with prehospital tracheal intubation in OHCA include a low

success rate, long duration of intubation attempts with interruption of chest compressions, and unrecognized tube misplacement or inadvertent esophageal insertion [27]. The total success rate of prehospital tracheal intubation performed by nonphysicians varies between 75 and 90% [26–28]. Jones and colleagues found that 5.8% of all patients intubated outside hospital had their tracheal tube outside the trachea [29]. Bair et al. reported a 2% incidence of incorrect positioning of the tracheal tube at admission to hospital, unrecognized by paramedics [30]. Other authors reported an even higher incidence of tracheal tube malpositioning—6.7% of esophageal intubation and 10.7% of endobronchial intubation [31]. The correct positioning of the tracheal tube inside the trachea should be always confirmed by an $etCO_2$ detection device. An esophageal detector device can be used to avoid esophageal placement [32]. Wang et al. evaluated the impact of intubation errors in the out-of-hospital setting on patient outcome [33]. One or more errors were reported in 22.7% of patients (failed tracheal intubation in 15%, multiple attempts in 3%, and tube malpositioning also in 3%). However, these errors were not directly linked to increased mortality. Difficulties with, and failures of, tracheal intubation in the prehospital environment may be caused by conditions which are often far from ideal—too little or too much light, patient position, and lack of space—and exacerbated by the low exposure of many paramedics to regular tracheal intubation. The average incidence of tracheal intubation performed by individual EMS providers is estimated at between 1 and 4 per annum [27, 34]. The incidence of difficult intubation in prehospital medicine is over 10%, with independent contributing factors being obstructed airway, intubation on the floor, and a distance between hyoid bone and tip of the chin less than 4.5 cm [35].

Attempts for tracheal intubation may cause significant interruption to chest compressions during CPR for OHCA. The median duration of interruptions caused by tracheal intubation was 109.5 s, with more than one-third of patients requiring more than two attempts for successful tracheal intubation [36]. Another study evaluated the number of attempts needed for successful tracheal tube placement in the prehospital setting [37]. More than one attempt was required in more than 30% of patients. Cumulative success rate in OHCA for the first three intubation attempts was 69.9%, 84.9%, and 89.9%, respectively. However, the success rate for tracheal intubation was significantly higher in OHCA patients than in the scenario of nonarrested subjects requiring sedation. Egly et al. studied the influence of prehospital intubation on survival of patients with OHCA [38]. Retrospective analysis included 1515 cases of OHCA. Patients with ventricular fibrillation or ventricular tachycardia who were intubated showed lower survival rate to discharge while, in the whole cohort, there was no difference found between intubated and nonintubated subjects.

Some countries, as Germany, Austria, or the Czech Republic, have physicians trained in anesthesia or emergency medicine available as part of a coordinated prehospital ambulance service response. The risks associated with tracheal intubation amongst these services are therefore lower, with the first pass and overall success rates being higher. Under these conditions, prehospital tracheal intubation may offer a benefit over other methods [39].

2.3.2. Supraglottic Airway Devices. Several studies have compared the insertion of a supraglottic airway device (SAD) with conventional tracheal intubation in cardiopulmonary resuscitation in the adult population. Percieved benefits of an alternative airway management using an SAD in cardiac arrest include a shorter time of device insertion and higher success rates than tracheal intubation when performed by paramedics and other nonanesthesiologists [23]. Most published studies are nonrandomized mainly due to ethical reasons.

Tanabe and colleagues performed a nation-based study of 318141 patients with OHCA [40]. Advanced airway management techniques were used in 43.5% and included esophageal obturator (63%), laryngeal mask airway (25%), and tracheal tube (12%). Both SADs were associated with significantly worse neurological outcome than tracheal intubation. Kajino et al. studied the influence of airway management technique on outcome in OHCA using a prospective cohort design [41]. In total, 5377 cases received advanced airway management following cardiac arrest (31.2% using tracheal intubation, 68.9% using a supraglottic airway device). There were no differences either in survival or incidence of good neurological outcome between devices, although tracheal intubation took a significantly longer time. Shin and colleagues studied the outcome of 5278 patients with OHCA whose airways were managed using bag-mask ventilation, tracheal intubation, or laryngeal mask airway [42]. The latter option showed the lowest rates of survival to hospital admission and also reduced survival to discharge from hospital. The main limitation of the study was the significant disproportion between the airway management techniques used (BMV 87.9%, TI 7.4%, and LMA 4.7%). Similar results were published by Wang et al. who performed a secondary analysis of data related to airway management from ROC PRIMED trial [43, 44]. Successful tracheal intubation was associated with better early survival and higher hospital discharge rates when compared to insertion of an SAD during OHCA [43].

It is appropriate to mention some limitations of SAD use during CPR for cardiac arrest. Laryngospasm is sometimes present in the early stages of cardiac arrest as a protective airway reflex against aspiration. Higher peak inspiratory pressures are necessary to overcome laryngospasm and may exceed the maximal seal pressure of the SAD device, causing a significant leak or ineffective ventilation [23]. During elective surgical procedures under general anesthesia major leak is seen only in 0–5% of cases [45, 46] while, during CPR, it may reach more than 20% [47, 48]. SADs are also ineffective in providing controlled ventilation in patients with very low chest compliance and high rigidity, as seen in drowning persons or in the advanced stages of cardiac arrest [49]. SADs furthermore provide only limited protection against aspiration of gastric fluid and very low protection against aspiration of solid gastric contents. However, most patients with OHCA aspirate before arrival of the EMS and before attempts for advanced airway management [50]. The 2nd

generation SADs such as the ProSeal LMA, Supreme LMA, and i-gel supraglottic airway [51] should theoretically provide better protection against aspiration of gastric contents. Insertion of the i-gel and Supreme LMA seems to be easier than with the LMA Classic [23]. The i-gel resuscitation pack has been developed specially for CPR scenarios and incorporates a side channel for passive delivery of oxygen [52], but clinical experience is so far very limited [53]. The i-gel airway has showed 100% insertion success rate in OHCA with 97% of patients receiving effective ventilation. Furthermore, insertion of the device did not cause any interruptions in chest compressions in 74% of victims [48]. Other SADs trialled in OHCA included laryngeal tube (85.3% insertion success rate), which was not considered to be an appropriate adjunct in CPR due to high incidence of failure and other complications [47], intubating LMA, LMA Supreme, LMA ProSeal, and CobraPLA. The Combitube has been trialled for prehospital airway management mainly in the United States. Wang et al. in their paper reported 1521 Combitube insertions in out-of-hospital scenarios (1.7% of all airway interventions) [27]. The Combitube has an overall insertion success rate almost 98% but its use may be associated with serious complications including esophageal perforation or airway trauma and has proven difficult to insert in people with neck immobilization with a cervical collar [54].

In conclusion, the laryngeal mask airways and the i-gel might be considered as alternate airway devices in OHCA. Other SADs have lower success rate or carry a higher risk of potentially serious complications.

2.3.3. Bag-Valve Mask Ventilation. Bag-valve mask ventilation (BMV) is a fundamental basic airway skill. During its application with a self-inflating bag, maintenance of a patent upper airway is mandatory. This can be achieved with a "triple maneuver" (jaw thrust and neck extension) or with the insertion of an oropharyngeal or nasopharyngeal airway [25]. BMV is an easy method, often applicable without difficulty by paramedics or even by laypersons. Using intermittent positive pressure ventilation, the main adverse effects associated with BMV are stomach distension, airway leak (up to 40%), and lack of protection of the airway against aspiration [50]. Regurgitation may occur in 12.4% of patients ventilated with BMV during OHCA while insertion of LMA may decrease this risk to 3.5% [50]. Another study showed an even higher incidence of this complication—20% of patients regurgitated at the scene and 24% of all resuscitated persons had radiological findings of aspiration on chest X-ray after admission to hospital [55]. All patients were intubated at the scene. A prospective population-based study (All-Japan Utstein Registry) evaluated 649,359 patients with OHCA [56]. Primary outcome of this trial was neurological outcome related to different airway management technique during CPR and prehospital emergency care after ROSC. In total, 57% of patients were managed using bag-mask valve ventilation while 37% of them had inserted a supraglottic airway device and only 6% underwent prehospital tracheal intubation. BMV was associated with a significantly higher chance for neurologically favorable outcome than tracheal intubation or supraglottic airway device insertion. No difference in terms of neurologically intact survival was reported between patients receiving tracheal intubation or a supraglottic airway device.

In another smaller study, a group of patients with OHCA managed using BMV showed a comparable rate of survival without neurological deficit compared to patients who underwent prehospital tracheal intubation [57].

2.4. Extracorporeal Oxygenation and Life Support. The term extracorporeal cardiopulmonary resuscitation refers mainly to the technique of venoarterial extracorporeal membrane oxygenation (VA-ECMO) [58]. This technique may be indicated in both out-of-hospital and in-hospital cardiac arrests, mainly those refractory to conventional CPR. Venous blood is led to a membrane oxygenator and then oxygenated blood returned to the arterial circulation of the victim. VA-ECMO is used as a bridging therapy in arrested patients with severely impaired ventricular function, until either their heart function improves or before utilization of a mechanical ventricular assist device [59]. The main prerequisite for the use of the VA-ECMO in cardiac arrest is undamaged or only minimally affected brain function [60]. The use of cardiopulmonary bypass in prolonged cardiac arrest was firstly described by Safar et al. in 1990 [61]. Extracorporeal support devices have undergone significant technological advances over the years in terms of simplicity, portability, and miniaturization.

Several studies have explored the efficacy of VA-ECMO in cardiac arrest in terms of mortality and neurological outcome. An initial report described up to 20% survival rate after in-hospital cardiac arrest of adult patients [62].

Three-month neurological outcome following CPR for nontraumatic cardiac arrest was evaluated in a cohort of 162 adult patients [63]. VA-ECMO was initiated in 53 patients while conventional CPR was used in the remaining 109 victims. Survival with neurologically unchanged brain function was significantly higher in the VA-ECMO group—29.2% versus 8.3% ($P = 0.018$). The only independent predictor associated with a favorable neurological outcome at 90 days was the diameter of the victim's pupils at time of hospital admission.

Reports evaluating the efficacy of extracorporeal CPR in adult OHCA were appraised in an article by Morimura et al [60]. The authors collected a sample of 1282 victims (from 105 articles) who received the VA-ECMO during CPR. The overall survival rate, including discharge from hospital, was 26.7%. Most surviving patients presented as neurologically intact or having a mild disability only.

Chen and colleagues performed a three-year prospective observational trial assessing the efficacy of VA-ECMO versus conventional CPR in witnessed in-hospital cardiac arrest [64]. They found a significantly higher 30-day survival rate, discharge rate from hospital, and 1-year survival rate in the extracorporeal support group.

Most centers have reported significantly lower survival of patients with out-of-hospital cardiac arrest treated with the VA-ECMO when compared with patients who had witnessed cardiac arrest of cardiac origin in hospital [65, 66].

Le Guen et al. in their study reported very low survival rates (4%) in patients supported with VA-ECMO following OHCA and recommended a rather restricted approach for its use for this indication [67].

ERC guidelines recommend consideration of extracorporeal life support in various scenarios, but not in out-of-hospital cardiac arrest of cardiac origin [6, 8]. AHA 2010 guidelines do not recommend extracorporeal life support techniques for routine use in patients with cardiac arrest. The use of extracorporeal techniques should be considered only in specialized centers and in persons with a good chance for neurological recovery [68].

2.5. Hyperventilation and the Effect of Positive Airway Pressure. Hyperventilation and intermittent positive pressure ventilation (IPPV) "per se" have negative effects on circulation during CPR and after ROSC [69]. Positive airway and intrathoracic pressures during the mechanical inspiration phase of the breathing cycle cause a significant decrease in venous return to the thoracic cavity, reducing preload to the right heart [70]. Hyperinflation results not only in a fall in cardiac output and performance of the right ventricle, but also cause a significant reduction in coronary perfusion pressure [69] enhancing hypotension [71]. In published studies, most paramedics ventilated patients at a higher frequency and at higher inspiratory pressures than recommended [72]. A special device—impedance threshold device (ITD)—has been developed in order to reduce intrathoracic pressures, with a resulting improvement in venous return and coronary blood flow during CPR [73, 74]. A valve inside the ITD closes during chest wall recoil and helps to create a negative intrathoracic pressure as low as −13 mmHg [75]. Various clinical studies have assessed the effect of ITD on survival and neurological outcome after OHCA. In total, seven randomized controlled trials have assessed the ITD in prehospital emergency care. A study by Plaisance et al. showed better coronary perfusion and higher diastolic pressures in patients treated with ITD valve [76] while another trial compared the use of ITD with a sham device during CPR in twenty-two patients with OHCA and showed marked improvement in systolic pressure in the ITD group [77]. Use of the ITD combined with active compression-decompression was associated with increased hospital admission and short-term survival rates [78, 79]. Aufderheide et al. compared ITD with a sham device during standard CPR in 230 patients [71]. The subgroup of people who presented with a pulseless electrical activity (PEA) showed higher 24 h survival, while there was no difference in patients with VF or asystole. A meta-analysis based on available trials [80] concluded that the use of ITD may improve short-term outcome after OHCA. None of the studies evaluated hospital discharge rate in terms of neurological deficit. A robust multinational study unfortunately did not confirm the conclusions of this meta-analysis [81]. The authors evaluated 8,718 patients with OHCA randomly allocated to an active treatment with ITD and to sham group and found no differences in survival, ROSC, or recovery without neurological dysfunction. Similar concerns were also reported by some animal studies. These trials reported either no positive effect of ITD [82, 83] or indeed a worse outcome in the ITD groups [84].

On the other hand, if an ITD is combined with active compression-decompression it improves hospital discharge with neurologically favourable outcome when compared with conventional CPR [78].

The real significance of clinical studies assessing the role of ITD in OHCA might be confused by the fact that some studies compared ITD use with conventional CPR only, whilst other studies implemented ITD application with the use of active compression-decompression CPR [81].

ERC guidelines do not recommend the routine use of the ITD due to a lack of data confirming its benefit in long-term survival of victims [6, 7]. AHA guidelines recommend consideration of ITD use by the staff familiar with the device during OHCA (level of evidence B, class IIb) [68].

3. Management after Resuscitation (Post-ROSC Period)

3.1. Hyperoxemia after Resuscitation. Hypoxemia has deleterious and potentially lethal effects on vitally important organs, mainly on the brain and myocardium. However, recent studies have shown that hyperoxemia may also have significant negative effects in the postcardiac arrest period, primarily on neurological outcome [10, 85]. Excessive oxygen is a precursor for reactive forms of oxygen (reactive oxygen species—ROS, oxygen free radicals—OFR) which are created after restoration of spontaneous circulation in the tissues as a part of ischemia-reperfusion injury [5]. Mainly superoxide, hydroxyl radicals, and peroxynitrite cause direct damage to the cells which may result in their worsened function or death.

Several animal trials and data from three human studies support this theory. The effect of different oxygen fraction on neurological outcome after experimental cardiac arrest in animals was firstly evaluated by Balan et al. 2006 [85]. The authors induced ventricular fibrillation in 17 dogs and then resuscitated them using open-chest CPR. The dogs were subsequently randomized to receive either 100% O_2 IPPV or controlled ventilation with FiO_2 adjusted according to pulse oximetry measurements (target spO_2 was 96%). In the hyperoxemic subgroup paO_2 rose to 75.2 (±4.8) kPa while, in the oximetry subgroup, it remained within the physiological range—12.5 (±0.5) kPa. Hyperoxemic dogs showed a higher incidence of neurological deficit at 23 hours, as well as a higher number of pathologically altered neuronal changes in the CA1 region of the dorsal hippocampus. Similar findings were also reported by Liu et al, who demonstrated better neurological recovery and a lower degree of lipid oxygenation in the brain at 24 h on a canine model of ventricular fibrillation in normoxemic animals (FiO_2 0.21) than in a hyperoxemic group (FiO_2 1.0) [86]. Vereczki et al. performed another study on a canine model of cardiac arrest and demonstrated that normoxemic animals in the post-ROSC period had a lower level of oxidative stress, decreased intraneuronal protein nitration, and a lesser extent of neuronal death in the hippocampus [87]. Another study performed on swine

model ventilated with 100% oxygen for 60 min after ROSC also showed a significantly higher degree of degeneration of neural cells in the striatum when compared with the group ventilated with FiO_2 0.21 10 minutes after ROSC [88]. These findings are, however, disputable because of the retrospective study design and insufficient number of probands.

Angelos et al. demonstrated a deleterious effect of post-ROSC hyperoxemia on a rat model. Sprague-Dawley rats exposed to high-concentration oxygen for 60 min presented with significantly impaired function of myocardial mitochondria when compared with normoxemic rats [89].

The first human trial related to the oxygen fraction in the postarrest period was published in 2006 [90]. In total, 28 patients who had witnessed OHCA were randomized to receive controlled ventilation with FiO_2 1.0 or 0.3, respectively, after the return of spontaneous circulation. Functional neurological status and biochemical markers of neuronal injury (neuron specific enolase—NSE, protein S100) were measured for up to 48 h after ROSC. There was a higher level of NSE at 24 h in the hyperoxemic group without any difference in mortality or neurological outcome. However, this study was significantly underpowered to detect changes in neurological status between the groups.

More human data comes from a retrospective analysis of 6,326 patients hospitalized in the ICU after CPR for cardiac arrest [10]. These persons were divided into the three groups—hypoxemia (PaO_2 less than 8.0 kPa), normoxemia (PaO_2 between 8.0 and 40 kPa), and hyperoxemia (PaO_2 more than 40 kPa). A significantly higher hospital mortality (63%) was demonstrated in the hyperoxemic patients, whilst the lowest mortality was seen in normoxemic victims (44%). Hyperoxemic patients also had the highest incidence of neurological deficit at hospital discharge.

However, these findings were questioned by two recent clinical studies [91, 92]. In total, 12,108 patients resuscitated from nontraumatic cardiac arrest were divided into three groups according to their PaO_2. The authors studied the outcomes of resuscitated adult patients divided into three groups according to their worst PaO_2 within 24 h after CPR. The hyperoxemic group showed slightly lower survival rate than normoxemic victims but after adjustments and Cox modelling the differences became statistically insignificant [91]. Spindelboeck and colleagues studied the outcome of resuscitated adult patients divided into three groups according to their PaO_2 at 60 min after commencing CPR. Hyperoxemic group showed higher survival rates to the hospital admission than normoxemic and hypoxemic groups but differences in neurologically intact survival rates were insignificant between the groups [92].

Another study explored the time frame of exposure to hyperoxemia after cardiac arrest [93]. The authors found that most patients were exposed to high values of PaO_2 in the immediate period after ROSC or during the following 24 hours, suggesting that the highest hyperoxemic values are associated with treatment in the prehospital phase and the Emergency Department. Furthermore, patients after OHCA had a higher incidence of hyperoxemia than patients after in-hospital cardiac arrest. As in other published studies, there have been extensive discussions over how to define hyperoxemia.

Based on this evidence, a lower targeted oxygen therapy (spO_2 or saO_2 between 94 and 98%) may be beneficial in the period after ROSC. Both resuscitation guidelines published recently—the American Heart Association (AHA) guidelines and European Resuscitation Council guidelines since 2010—highlight the harmful effect of hyperoxemia after ROSC. They recommend consideration of a normoxemic strategy controlled by spO_2 (94–98%) or saO_2 monitoring [6, 7].

3.2. Ventilation and Carbon Dioxide Tension after ROSC. Controlled ventilation affects carbon dioxide (CO_2) tension in the vascular system. Cardiac arrest is typically associated with profound metabolic acidosis. Previously, strategies have recommended hyperventilation after ROSC with the aim of decreasing $PaCO_2$ and thus stabilizing the pH of arterial blood. However, a deleterious effect on brain circulation is seen if hyperventilation results in hypocapnia [94]. Cerebral hyperperfusion occurs immediately after ROSC and can persist for up to 30 minutes. The subsequent period is characterized by significantly reduced cerebral blood flow. Hypocapnia during this period potentiates vasoconstriction, which can further aggravate postresuscitation hypoxic brain injury [7]. On the other hand, insufficient CO_2 removal is associated with hypercapnia contributing to the vasodilation of cerebral vessels and elevated intracranial pressure (ICP).

Falkenbach et al. highlighted the effect of postresuscitation therapeutic hypothermia on $PaCO_2$ level [95]. Hypothermia decreases metabolic rate and carbon dioxide production. In their multicenter study, approximately 45% of patients experienced hypocapnia or hypercapnia, both of which negatively affect brain perfusion. The results of this study support the necessity of frequent and regular optimization of ventilator settings in the first 48 hours after OHCA. A number of studies have evaluated the effects of hypercapnia and hypocapnia on outcomes in adult patients after cardiac arrest. The database of the Australian and New Zealand Intensive Care Society (16,542 patients) has shown higher mortality and lower discharge rates in hypocapnic patients when compared with normocapnic and hypercapnic victims [96]. Roberts and colleagues analyzed adult cardiac arrest registry data from 193 victims and found that 69% of them experienced pathological values of $PaCO_2$ after OHCA [97]. Both hypocapnia and hypercapnia were associated with worsened neurological outcome. Lee et al. studied the relationship between blood gas tensions and outcome in 213 patients after OHCA treated with therapeutic hypothermia [98]. Hypocapnia was associated with higher in-hospital mortality; both hyperoxemia and hypoxemia were associated with worsened neurological outcome.

ERC guidelines suggest maintaining normocapnia during postresuscitation care [6]. AHA 2010 guidelines recommend monitoring of CO_2 tension with capnography and arterial blood gas analysis and keeping its level within the physiological range ($PaCO_2$ 40–45 mmHg; $PetCO_2$ 35–40 mmHg) [7].

4. Conclusions

During last decade, many papers have evaluated the issues of respiration, oxygenation, and airway management in OHCA. Some of them have been high-quality randomized controlled trials, moving the science of resuscitation forward and changing established algorithms and resuscitation protocols. The main finding arising from these studies is that, in OHCA of cardiac origin in adults, significantly interrupting chest compressions for the purposes of advanced airway management have a negative impact on patient survival and neurological outcome [36, 99]. These findings have prompted changes in BLS of adult patients with OHCA of nontraumatic origin. CAB (circulation-airway-breathing) has evolved from ABC [100] with the development of a new resuscitation philosophy—cardiocerebral resuscitation (CCR) [101, 102].

Passive oxygenation has its advocates, but one can object that its main beneficial effect is actually in minimizing the interruption of chest compressions in comparison with advanced airway management techniques.

The role of extracorporeal techniques on survival in patients after OHCA remains unclear. A few studies have demonstrated its benefit in patients with persisting cardiac arrest and with reactive pupils, though other trials have failed to report any significant benefit with this technique.

The choice of airway management technique in OHCA remains controversial. Although bag-valve mask ventilation has been repeatedly associated with better survival—including better neurological function than advanced techniques of airway management, the risk of regurgitation and aspiration cannot be underestimated. Tracheal intubation in the hands of experienced operators is still a reliable method. The evidence would suggest, however, that it should not be employed by individuals with low skills, limited experience, or infrequent exposure [37, 103]. The insertion of a supraglottic airway device in OHCA is probably associated with worse patient outcomes than other methods of airway management.

A few studies have explored the harmful effects of hyperoxemia, hyperventilation, and excessive chest inflation on patient outcome following OHCA. A significant number of these studies were performed on animal models with a small number of probands, and their interpolation to humans is difficult [104, 105]. Initial studies related to the use of an impedance threshold device (ITD), which protects against lung hyperinflation and helps to create a negative intrathoracic pressure, were promising in patients with OHCA of cardiac origin [73]. Unfortunately, a recent large trial did not show any beneficial effect of ITD on long-term survival with good neurological function [81].

The deleterious effects of pathological $PaCO_2$ values after ROSC on neurological outcome have been repeatedly described. Dyscarbia is a very common finding during therapeutic hypothermia in the postresuscitation period due to the decreased metabolic demand of patients [95]. Clinicians should maintain $PaCO_2$ in the upper physiological values after ROSC.

Abbreviations

AHA: American Heart Association
ALS: Advanced life support
ATP: Adenosine triphosphate
BLS: Basic life support
BMV: Bag-valve mask ventilation
CCR: Cardiocerebral resuscitation
CFIO: Constant flow insufflation of oxygen
COCPR: Chest compression-only cardiopulmonary resuscitation
CPR: Cardiopulmonary resuscitation
DO_2: Oxygen delivery
ECMO: Extracorporeal membrane oxygenation
ERC: European Resuscitation Council
ICU: Intensive care unit
IPPV: Intermittent positive pressure ventilation
ITD: Impedance threshold device
LMA: Laryngeal mask airway
NSE: Neuron-specific enolase
OHCA: Out-of-hospital cardiac arrest
ROS: Reactive oxygen species
ROSC: Restoration of spontaneous circulation
SAD: Supraglottic airway device
VF: Ventricular fibrillation
VT: Ventricular tachycardia.

Disclosure

Pavel Michalek has lectured for several companies manufacturing supraglottic airway devices including Intersurgical Ltd., AMBU Ltd. and Intavent Orthofix Ltd.

Conflict of Interests

Tomas Henlin, Tomas Tyll, John D. Hinds and Milos Dobias declare no conflict of interests regarding the publication of this paper.

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Research Article

Impaired Cerebral Mitochondrial Oxidative Phosphorylation Function in a Rat Model of Ventricular Fibrillation and Cardiopulmonary Resuscitation

Jun Jiang,[1,2] Xiangshao Fang,[2,3] Yue Fu,[1,2] Wen Xu,[2,3] Longyuan Jiang,[2,3] and Zitong Huang[2,3]

[1] *Department of Emergency Medicine, The First People's Hospital of Foshan, 81 Ling Nan Road, Foshan, Guangdong 528000, China*
[2] *Institute of Cardiopulmonary Cerebral Resuscitation, Sun Yat-sen University, 107 Yan Jiang Xi Road, Guangzhou, Guangdong 510120, China*
[3] *Department of Emergency Medicine, Sun Yat-sen Memorial Hospital of Sun Yat-sen University, 107 Yan Jiang Xi Road, Guangzhou, Guangdong 510120, China*

Correspondence should be addressed to Yue Fu; drfuyue@gmail.com

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Postcardiac arrest brain injury significantly contributes to mortality and morbidity in patients suffering from cardiac arrest (CA). Evidence that shows that mitochondrial dysfunction appears to be a key factor in tissue damage after ischemia/reperfusion is accumulating. However, limited data are available regarding the cerebral mitochondrial dysfunction during CA and cardiopulmonary resuscitation (CPR) and its relationship to the alterations of high-energy phosphate. Here, we sought to identify alterations of mitochondrial morphology and oxidative phosphorylation function as well as high-energy phosphates during CA and CPR in a rat model of ventricular fibrillation (VF). We found that impairment of mitochondrial respiration and partial depletion of adenosine triphosphate (ATP) and phosphocreatine (PCr) developed in the cerebral cortex and hippocampus following a prolonged cardiac arrest. Optimal CPR might ameliorate the deranged phosphorus metabolism and preserve mitochondrial function. No obvious ultrastructural abnormalities of mitochondria have been found during CA. We conclude that CA causes cerebral mitochondrial dysfunction along with decay of high-energy phosphates, which would be mitigated with CPR. This study may broaden our understanding of the pathogenic processes underlying global cerebral ischemic injury and provide a potential therapeutic strategy that aimed at preserving cerebral mitochondrial function during CA.

1. Introduction

Postcardiac arrest brain injury is a common cause of morbidity and mortality in postcardiac arrest patients [1], leading to death in 68% of patients after out-of-hospital cardiac arrest [2] and significant cerebral dysfunction in survivors [1]. Brain tissue is especially susceptible to ischemic injury due to several unusual features of its energy metabolism, including a high metabolic rate, limited intrinsic energy stores, and critical dependence on aerobic metabolism of glucose.

Recently, accumulating data have shown that mitochondria, the crucial cellular organelles for energy production, play a critical role as effectors and targets of ischemia and reperfusion injury after cardiac arrest (CA) [3, 4]. Previously, our group [5] and others [6–8] have demonstrated the impaired myocardial mitochondrial dysfunction and ultrastructural alterations of mitochondria developed during CA and following return of spontaneous circulation (ROSC). These observations suggested that an impaired functional capacity of myocardial mitochondria plays a pivotal role in the development of postresuscitation myocardial dysfunction. More recently, Gazmuri et al. reported that the strategies of preserving mitochondrial bioenergetic function in the myocardium by using inhibitors of the sodium-hydrogen

exchanger isoform-1 [9–12] and erythropoietin [13–15] help restore cardiac activity and sustained postresuscitation circulation.

However, there is a lack of sufficient evidence regarding mitochondrial dysfunction and energy metabolic derangements during CA and following cardiopulmonary resuscitation (CPR). Previously, studies had reported that mitochondrial dysfunction was impaired 1 h after successful resuscitation in an aging rat model study [16]. At present, our knowledge regarding mitochondrial function and energy metabolism following global cerebral ischemia is largely extrapolated from other specific experimental settings such as focal cerebral ischemia [17–19]. Because of many significant pathophysiological differences between these heterogeneous experimental settings, it is unknown whether these settings and CA/CPR share common mechanisms. The changes in cerebral metabolic activity during CA may therefore differ from those described in other experimental settings. The aim of the present study was to provide further insight into the cerebral mitochondrial dysfunction and energy metabolic disorders during CA and CPR.

Thus, the current study was undertaken in a rat model of CA to test the hypothesis that prolonged VF will lead to significantly impaired functional capacity of cerebral mitochondria and complete depletion of high-energy nucleotides. Furthermore, we hypothesized that CPR with optimal chest compressions and mechanical ventilation could significantly ameliorate these cerebral mitochondrial defects and metabolic disorders.

2. Method

All experimental procedures were approved by the Animal Experimentation Ethics Committee, Sun Yat-sen University, and were consistent with the Guidelines for Ethical Conduct in the Care and Use of Experimental Animals published by the Chinese Ministry of Science.

2.1. Animal Preparation. Healthy, male Sprague-Dawley rats weighing 350–450 g fasted overnight before surgery (they were given free access to water). Sodium pentobarbital was administered intraperitoneally at 45 mg kg^{-1} to provide anesthesia, and a number 14 tracheal sheath was directly inserted through the mouth of each rat. A number 23 PE-50 catheter was inserted into the left femoral artery to monitor mean arterial pressure (MAP). A 3-French catheter was inserted into the right external jugular vein to guide the guide wire (anode) to the inner membrane of the right ventricle, and a needle (cathode) was inserted subcutaneously to form a loop and induce VF. The Windaq data acquisition system (DataQ, Akron, OH, USA) was used for continuous monitoring of MAP and electrocardiography (ECG). Rectal temperature was monitored continuously, and a heating lamp was used to maintain animal body temperature at 37.0 ± 0.5°C. Before onset of VF, an Abbott bedside blood gas analyzer was used to examine the arterial blood gas of the test animals.

2.2. Experimental Procedure. The experimental rats were randomly divided into the following three groups of 20 each: (1) sham group: anesthesia, endotracheal intubation, and insertion of arterial and venous catheters were performed, and VF was not induced; (2) ischemia group: VF-induced CA for 15 min, no CPR; (3) CPR group: VF-induced CA for 10 min, and CPR was performed for 5 min.

Before induction of VF, the animals were mechanically ventilated with room air at a tidal volume of 0.55 mL/100 g and a frequency of 80 breaths/min. A progressive increase in 60 Hz current to a maximum of 3 mA was then delivered to the right ventricular endocardium. The current flow was continued for 3 min to preclude spontaneous reversal of VF. Mechanical ventilation was discontinued after onset of VF. For the CPR group, 5 min of CPR including precordial compressions and mechanical ventilation with 100% O_2 was then performed 10 min after the onset of VF. Precordial compressions at a rate of 250 min^{-1} were synchronized to provide a compression/ventilation ratio of 5 : 1. Depth of compression was adjusted to maintain an aortic diastolic pressure of 26 to 28 mmHg. In the ischemia group, no CPR was attempted, resulting in 15 min of untreated VF. After 15 min of treated or untreated VF, all animals were immediately sacrificed. Measurement of mitochondrial oxidative phosphorylation parameters was performed in 8 animals for each group by an investigator who is not responsible for the isolation of brain mitochondria. Determination of adenine nucleotides and lactate content by high-performance liquid chromatography (HPLC) was performed in additional 8 animals per group by an independent experienced technician. In addition, neuronal mitochondria were analyzed in a blinded manner for qualitative ultrastructural changes (compared with sham control) in another 4 animals for each group by an experienced pathologist trained in EM who is unrelated to the present study.

2.3. Isolation of Brain Mitochondria. The rats were decapitated and bilateral hippocampus brain tissues and equal amounts of cortical tissues were separated rapidly, weighed, and placed in an ice-cold Dounce homogenizer. Mitochondrial separation medium (215 mM mannitol, 75 mM sucrose, 0.1% bovine serum albumin, 20 mM HEPES, 1 mM EGTA, adjusted to pH 7.2) was added at volume ratio 1 : 10, and 10 rounds of homogenization were performed (six with tight fitting pellets and four with loose fitting pellets) to ensure that no chunks of brain tissue remained. The homogenized tissue mixture was then subjected to centrifugation at 1,300 g for 4 min (4°C). The supernatant was centrifuged at 12,000 g for 8 min, and precipitate was resuspended and again centrifuged at 12,000 g for 8 min. Then the supernatant was discarded, and separation medium without EGTA was added at a volume ratio of 1 : 0.4 to resuspend the mitochondria. This mitochondria suspension was then stored in an ice bath until testing. A Qubit fluorometer (Invitrogen, Carlsbad, CA) was used to measure the protein concentration of each sample. All these operations were performed in a 0–4°C ice bath.

2.4. Determination of Mitochondrial Oxidative Phosphorylation Parameters. A Clark oxygen electrode system (OxygraphTM, Hansatech Instruments, King's Lynn, UK) was used to test the mitochondrial oxidative phosphorylation function. In a sealed reaction tank, 2.5 mL reaction buffer (225 mM mannitol, 125 mM KCl, 4 mM $MgCl_2$, 0.1% BSA, 2.5 mM KH_2PO_4, 20 mM HEPES, pH 7.4, 25°C) was added and stirred fully to a steady state. Then, 20 μL mitochondrial suspension was added for 1 min until the recorded curve stabilized. Next, 20 μL disodium succinate (4 mM) was added, and the oxygen concentration declined slowly; the measured rate of oxygen consumption indicated respiratory state 4 (R4). Then, 20 μL adenosine diphosphate (ADP, 50 mM) was added, and the oxygen concentration showed a rapid decline. The measured rate of oxygen consumption indicated state 3 respiration (R3). The unit of mitochondrial respiration rate was oxygen consumption per nM/min/mg protein. The mitochondrial respiratory control ratio (RCR) was a ratio of state 3 and state 4 (R3/R4). RCR indicates the integrity of the membraneand oxidative phosphorylation in the mitochondrion, and the decrease of RCR suggests impaired mitochondrial function.

2.5. Measurement of Phosphocreatine (PCR), Adenosine Triphosphate (ATP), and Lactate Content. The brain tissue was prepared according toPontén et al. [20]. The rats were immersed in liquid nitrogen from head to shoulders for 5 min for fast and complete freezing of the brain tissues. Then, their heads were cut off. In a −20°C freezer, bilateral hippocampal and cortical tissues were rapidly separated and stored in liquid nitrogen. HPLC was used to determine the concentrations of PCr, ATP, and lactate in the brain tissues. The frozen brain tissue samples were homogenized in 0.3 M perchloric acid (1 mg : 6 μL). The suspension was collected and subjected to centrifugation at 3,000 rpm for 5 min (4°C). The supernatants were collected, the pH was adjusted to 7.6–7.8 with 0.5 M KOH solution, and then the mixture was again subjected to centrifugation at 3,000 rpm for 5 min (4°C). The supernatants were collected and stored in liquid nitrogen. An Agilent Technologies 1200 Series HPLC analyzer (Germany) was used to test the samples. A WATERS C18 reversed-phase HPLC column was selected, and KH_2PO_4 solution (200 mM), 10% acetonitrile, and TBA solution (3 mM) were used to prepare the mobile phase, and the pH was adjusted to 6.5 or 6.8, respectively. The concentrations of lactate and PCr were measured at an absorption peak of 210 nm and mobile phase pH 6.5. The concentration of ATP was measured at an absorption peak of 260 nm and mobile phase pH 6.8.

2.6. Observation of Ultrastructure Using Electron Microscope. A catheter was placed in the carotid artery of the anesthetized rat, and the right atrial appendage was cut open. Fixative solution (pH 7.4, precooled to 4°C), made of 2.5% glutaraldehyde and 2% paraformaldehyde, was perfused through the carotid artery. The hippocampal CA1 and cortical area were isolated, fixed with 1% osmium tetroxide, and then dehydrated and embedded in epoxy resin. According to the standard principle of three-dimensional localization, 80 nm sections were randomly cut, mounted on copper mesh, double stained with lead citrate and uranyl acetate, and then placed under transmission electron microscope for observation of the ultrastructure. Images were recorded.

2.7. Statistical Analysis. Measurement data was reported as mean ± standard deviation. For comparison of mean values among multiple groups, single-factor analysis of variance was performed. For comparison of mean values between two groups, the least significant difference t-test (LSD t-test) was performed. $P < 0.05$ was considered statistically significant. All analyses were performed using the SPSS statistical software package. Because PCr and lactate data failed the homogeneity of variance test, logarithmic transformation of the data was performed to satisfy homogeneity of variance before further analyses.

3. Results

3.1. Basic Physiological Parameters and Hemodynamics. The body weights, blood gas values before resuscitation, and baseline hemodynamic parameters did not show significant differences between the three groups of animals (Table 1). At the end of 15 min of CA, the aortic diastolic pressure in the CPR group was maintained between 26 and 28 mmHg as previously described, whereas the aortic pressure in the ischemia group was maintained at approximately 10 mmHg due to the remaining elastic properties of the arterial wall.

3.2. Determination of Mitochondrial Respiratory Function. RCR reflects the efficiency of oxidative phosphorylation and is closely related to mitochondrial function. The results showed the hippocampal and cortical R3 of the ischemia group to be significantly lower than those of the sham group ($P < 0.01$). The cortical R4 of the ischemia group was significantly lower than that of the sham group ($P < 0.05$). The RCR of the ischemia group was 53% (hippocampus) and 51% (cortex) lower than that of the sham group. The hippocampal and cortical R3 of the CPR group was significantly lower than that of the sham group, but it was significantly higher than that of the ischemia group ($P < 0.01$). The R4 of the CPR group tended to be lower than that of the ischemia group. The RCR of the CPR group was 20% (hippocampus) and 19% (cortex) lower than that of the sham group, but it was significantly higher than that of the ischemia group ($P < 0.01$). This suggests that CPR protects the mitochondrial respiratory function of rat neurons during CA. There was no significant difference in mitochondrial respiratory function between hippocampal and cortical tissues (Figure 1). Figure 2 showed the typical mitochondria respiration trace in hippocampus, depicting the sequence of substrate additions and subsequent oxygen utilization rates. Similar mitochondrial respiration traces were observed in cortex.

3.3. Energy Metabolism of Brain Tissues. As shown in Table 2, the PCr and ATP contents of the hippocampal and cortical tissues in the ischemia group were significantly lower than those in the sham group ($P < 0.01$), and the decrease in

Table 1: Basic physiological parameters and hemodynamic values of the three groups ($n = 20$).

	Sham group	Ischemia group	CPR group
Weight (g)	404 ± 26	403 ± 28	400 ± 31
Arterial pH	7.42 ± 0.05	7.45 ± 0.06	7.43 ± 0.05
Arterial PO_2 (mmHg)	91.60 ± 4.32	93.10 ± 5.88	92.15 ± 4.76
Blood serum lactate (mmol/L)	0.63 ± 0.08	0.59 ± 0.07	0.59 ± 0.08
Heart rate (bpm)	297 ± 20	303 ± 20	299 ± 19
MAP (mmHg)	140 ± 15	145 ± 15	146 ± 16

Note: there were no significant differences in each group.

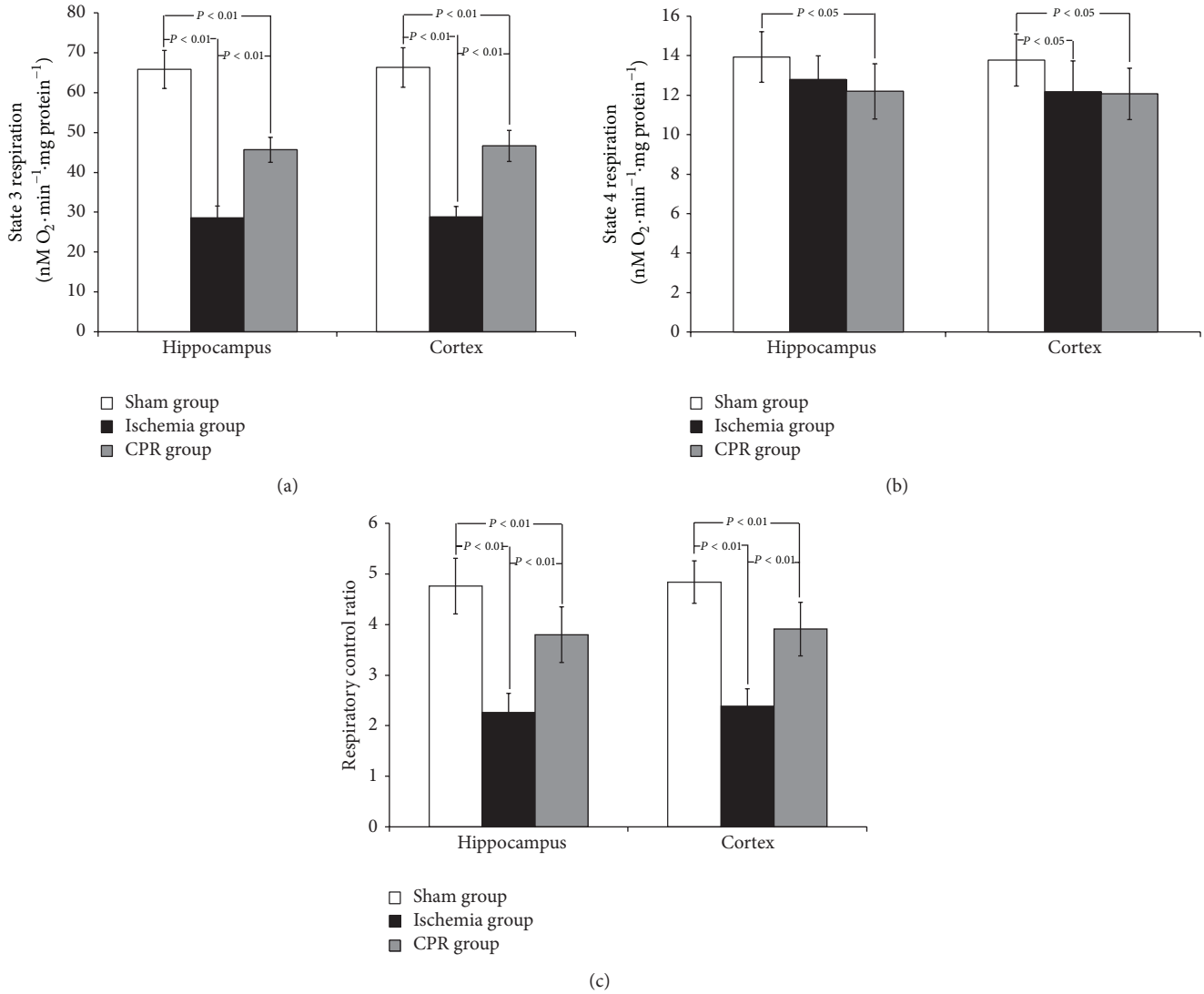


Figure 1: Comparison of mitochondrial respiratory parameters in different parts of the brain among groups ($n = 8$). Values are means ± SD.

PCr content was more substantial. The lactate content of the ischemia groups was significantly higher than that of the sham group ($P < 0.01$). After 15 minutes of ischemia, the hippocampal PCr and ATP levels of the ischemia group were 4.93% and 14.02% that of the sham group, respectively. The cortical PCr and ATP contents of the CPR group were 5.66% and 15.18% that of the sham group, respectively. The variance in the PCr, ATP, and lactate levels was more pronounced in the hippocampus than in the cortical tissues, but the differences were not significant. The PCr/ATP ratio of the ischemia group was significantly lower than that of the sham group ($P < 0.01$).

Compared with the sham group, the PCr and ATP levels in hippocampal and cortical tissues of the CPR group were

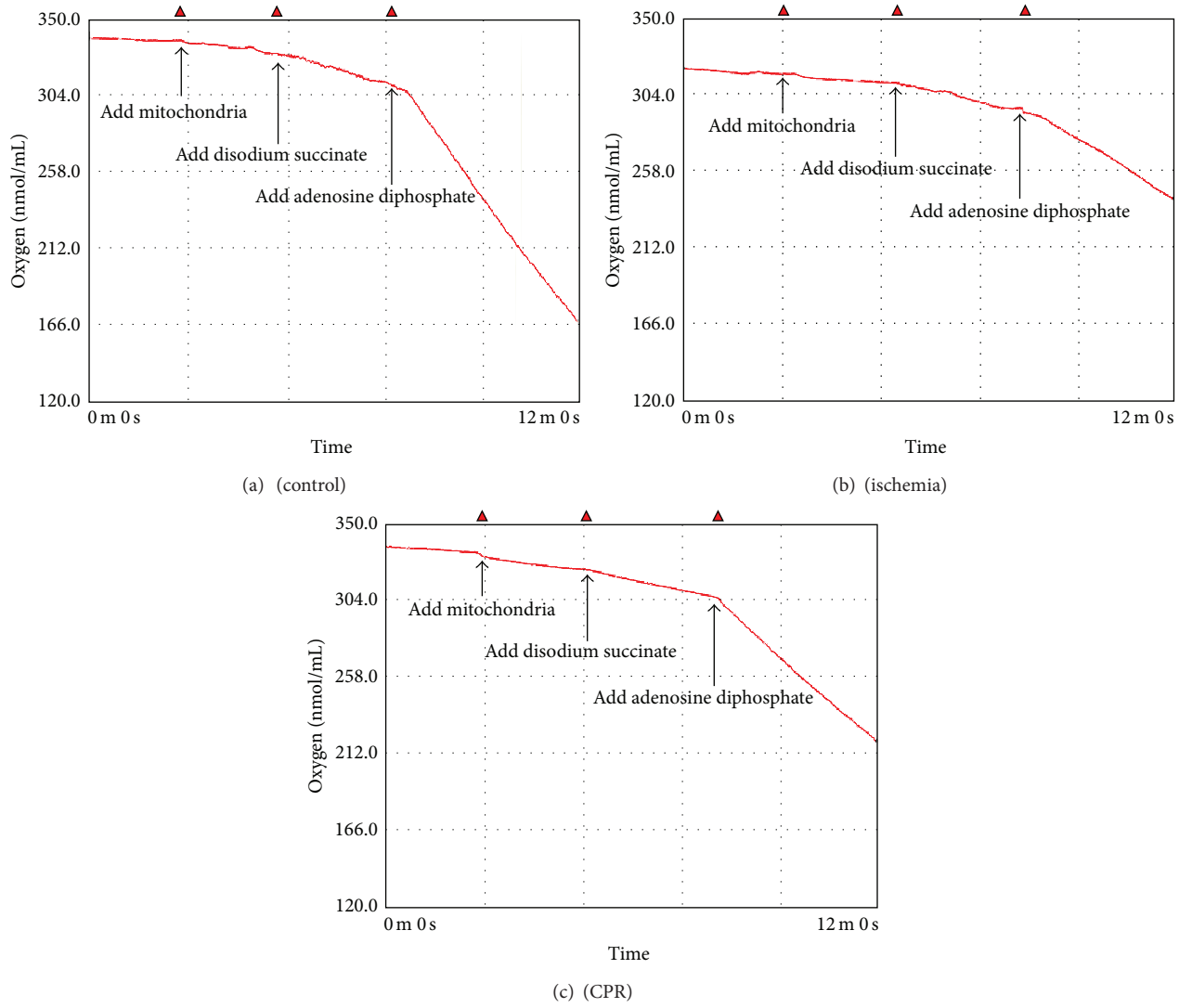


Figure 2: Representative oxygraph respiratory traces of hippocampal mitochondria.

Table 2: Energy metabolism in different parts of the brain among groups ($n = 8$).

	Hippocampus			Cortex		
	Sham group	Ischemia group	CPR group	Sham group	Ischemia group	CPR group
PCr (μM/g)	3.65 ± 0.25	0.18 ± 0.04**	1.24 ± 0.14$^{**\#}$	3.89 ± 0.27	0.22 ± 0.05**	1.31 ± 0.11$^{**\#}$
ATP (μM/g)	2.14 ± 0.15	0.30 ± 0.07**	0.85 ± 0.09$^{**\#}$	2.24 ± 0.12	0.34 ± 0.07**	0.82 ± 0.11$^{**\#}$
Lactate (μM/g)	0.97 ± 0.08	14.32 ± 1.32**	9.03 ± 1.07$^{**\#}$	1.02 ± 0.09	13.90 ± 1.05**	9.37 ± 1.22$^{**\#}$
PCr/ATP	1.71 ± 0.12	0.59 ± 0.07**	1.46 ± 0.17$^{**\#}$	1.73 ± 0.10	0.64 ± 0.06**	1.61 ± 0.12$^{*\#}$

$^{*}P < 0.05$ versus sham group; $^{**}P < 0.01$ versus sham group; $^{\#}P < 0.01$ versus ischemia group.

significantly lower ($P < 0.01$), but they were significantly higher than in the ischemia group ($P < 0.01$). The lactate content of the CPR group was significantly lower than that of the ischemia group ($P < 0.01$). The hippocampal PCr and ATP levels of the CPR group were 33.97% and 39.72% that of the sham group, respectively. The cortical PCr and ATP contents of the CPR group were 33.68% and 36.61% that of the sham group, respectively. These results suggest that CPR can significantly increase the concentration of high-energy phosphate compounds and reduce the concentration of lactate in brain tissues and so improve brain energy metabolism during CA in rats. The PCr/ATP ratio of the CPR group was significantly lower than that of the sham group ($P < 0.05$), but it was significantly higher than that of the ischemia group ($P < 0.01$).

3.4. Ultrastructure of Mitochondria. To assess the morphological changes, the ultrastructures of the hippocampal and cortical mitochondria in different groups were observed. The results did not show any notable structural damages in any

of the groups. Specifically, the mitochondria were round or oval. The mitochondrial structure was clear with complete inner and outer membranes. The electron density in the matrix was uniform, and the matrix had abundant cristae that were aligned nicely. There were no substantial morphological differences in the mitochondria among different groups (Figure 3).

4. Discussion

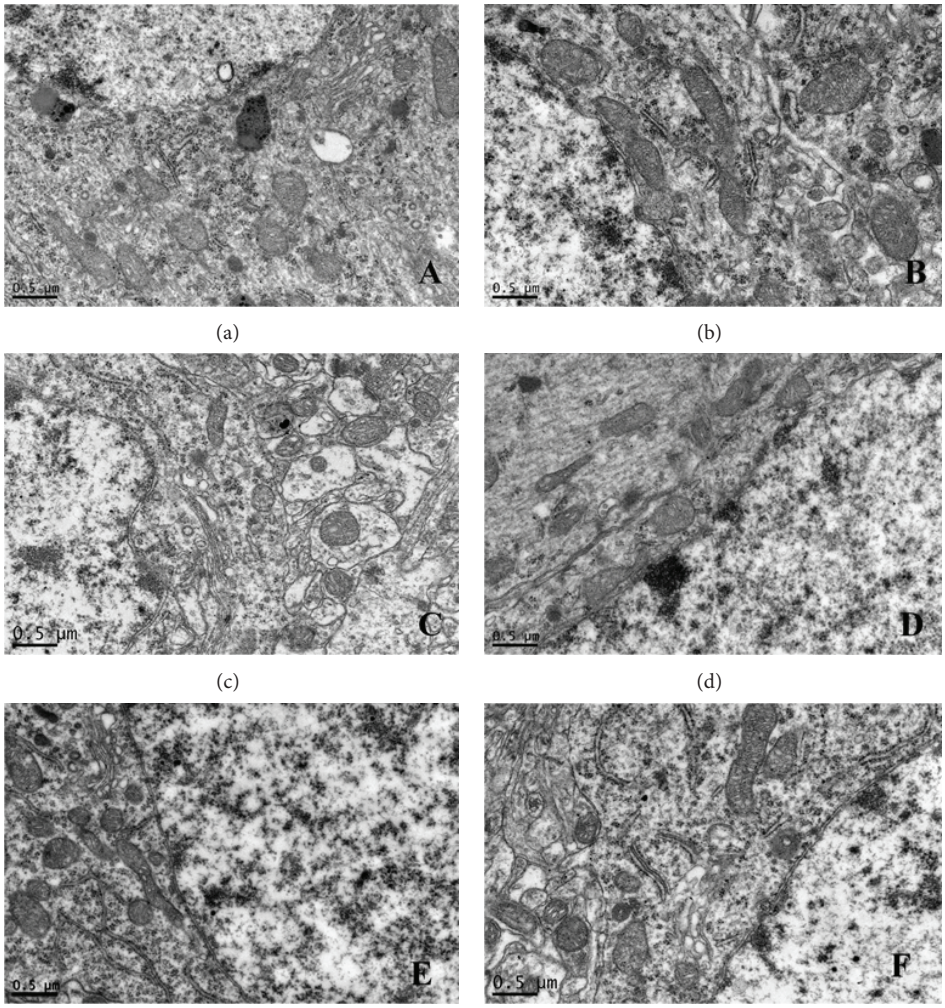
In the present study, using a rat model of prolonged VF, we demonstrated that metabolic derangements including impairment of mitochondrial respiration and partial depletion of ATP and PCr developed in the cerebral cortex and hippocampus following an untreated 15 min CA. Furthermore, CPR including closed chest compression and ventilation cannot only ameliorate the deranged phosphorus metabolism but more importantly protect cerebral mitochondrial function as well.

To describe possible alterations of high-energy phosphate compounds in the brain, it is essential to freeze the sample as quickly as possible, due to their extreme lability. Otherwise, delayed cooling will immediately result in hydrolysis of metabolites and erroneous depletion of ATP and PCr. In view of this, a well established *in situ* freezing technique [20] was employed in this study to avoid postmortem alterations in metabolites. Our results showed that baseline levels of the adenylate nucleotides and PCr detected in our experiment are similar to those previously published data [21], which provided the rational basis for further consideration. The mammalian structure is heterogeneous; therefore, previous studies have suggested that the metabolic rate and energy expenditure might be inconsistently apportioned among various regions [21]. In contrast to those reports, no significant differences in metabolic profile between the hippocampus and cortex were observed in this study.

The dynamic metabolite profile analysis of the VF animals verified that a progressive and severe cerebral energy failure develops when CA occurs and cerebral blood flow ceases, which was manifested by the breakdown of high-energy phosphates and the increased lactate formation as a consequence of increased anaerobic glycolysis. Currently, it is widely accepted that cerebral ATP stores will be exhausted within 5 min in sudden normothermic CA [22]. Previous studies by one group [23–26] and others [27], which examined metabolites by enzymatic fluorometric techniques, had proven that asystolic CA caused the ATP and PCr values to plummet to near zero within 5–10 min. Interestingly, it was unexpected to see that ATP, which was supposed to be at an undetectable level after 15 min of VF, was merely reduced to 14.02% in the hippocampus and 15.18% in the cortex of control animals. This retarded rate of ATP depletion may be due to the buffering effect of PCr; that is, ATP levels are initially preserved at the expense of PCr [28, 29]. Several investigations conducted by different groups supported our findings. In a perinatal rat model of hypoxia-ischemia, a more modest decline in ATP and PCr, assayed either by nuclear magnetic resonance spectroscopy or HPLC, has been observed with the observing time ranging from 5 min to 20 min [29–32]. Very recently, using bioluminescent methods,Seidl et al. [28] showed that myocardial ATP was depleted to less than 50% during the first 10 min of ischemia in a comparable rat model of VF. These discrepancies regarding the decline in energy expenditure metabolic rate in brain tissue after global ischemia may result from a variety of factors, such as the severity of the ischemic insult in different experimental procedure, the age/maturity of experimental animals, and the accuracy and sensitivity of the techniques adopted for measurement of the phosphate compounds. Here, we observed that ATP in the brain tissue determined by HPLC drastically but not totally decayed, suggesting the partially preserved neuronal viability after 15 min of untreated prolonged VF. Therefore, our finding indicated that even after a prolonged CA, the neurological functional integrity after damage from CA still has the potential to be minimized or reversed when cerebral blood flow can be adequately maintained following ROSC.

The major finding of the present study is that mitochondrial respiratory function in the brain declines after CA as shown by the respiratory control ratio (RCR) values, which is consistent with the trend of decay of high-energy phosphates. We believe that insufficient fuel and oxygen supply due to circulatory collapse are the leading causes that contribute to the cerebral metabolic failure. However, based on our observations of reduced mitochondria respiratory function and coincidently decreased high-energy phosphate compounds, it is reasonable to conclude that such defects in mitochondrial function are at least partly responsible for the metabolic failure during CA and resuscitation. Our group has previously reported myocardial mitochondrial abnormalities of ultrastructure and incapability in utilizing energy substrates and producing energy in this same animal model [5]. Other investigators have also reported early myocardial mitochondrial dysfunction after CA [33, 34]. However, limited data are available regarding the cerebral mitochondrial dysfunction during CA and following ROSC. Research by Xu et al. showed that RCR decreased by 26% in the cortex and 28% in the brainstem 1 h after resuscitation in an aging rat model of KCl-induced CA [16]. However, currently there is a lack in data revealing the cerebral mitochondrial dysfunction during CA and CPR and their relationship with changes in levels of high-energy phosphate. Therefore, our study provides evidence for the first time that reveals that an impairment mitochondrial function develops following CA and resuscitation, which may contribute to the global neurological dysfunction.

The physiological mechanisms responsible for mitochondrial dysfunction following ischemia remain unclear. It has been suggested that significant reductions in mitochondrial respiratory complex I activity are the major determinant of postresuscitation mitochondrial dysfunction [16]. Several factors, including reduction of the hydrophilic flavoprotein subunit and NADH-ferricyanide reductase, tissue acidosis, loss of flavin mononucleotide, and ATP depletion may account for the decrease in complex I activity [16, 35, 36]. However, the exact cellular and molecular mechanisms



(a) (b) (c) (d) (e) (f)

Figure 3: Electron micrographs in different parts of the brain among groups (magnification 23,000x). (a) Hippocampus of the sham group; (b) hippocampus of the ischemia group; (c) hippocampus of the CPR group; (d) cortex of the sham group; (e) cortex of the ischemia group; (f) cortex of the CPR group. Scale bars: 0.5 μm.

involved in this cerebral mitochondrial dysfunction following CA and CPR are not clear and deserve further investigation.

With respect to the morphological changes of mitochondria, ultrastructural alterations of myocardial mitochondria including swelling, edema, outer-membrane rupture, and loss of inner-membrane cristae with amorphous densities have been reported by our group and others [5, 33, 34] during CA and CPR, either in the VF or asphyxia CA rat model. To our surprise, we observed no significant ultrastructural morphological changes of cerebral mitochondria even following this prolonged untreated VF, when severely impaired mitochondrial function and reduction of high-energy phosphates were observed. The fact that the shape of mitochondria appeared relatively normal in this study suggests that although the cerebral mitochondrial function is impaired, the neurocytes might be salvageable after restoration of adequate cerebral blood flow.

Comparison between the CPR and VF groups shows that a period of 5 min CPR after 10 min of VF can lead to less mitochondrial damage and better energy preservation. Our study indicated that CPR can slow the ongoing ischemic insult imposed on mitochondrial bioenergetic function and possibly extent the viability of brain after CA. These observations are compatible with previous studies that reported that CPR can preserve myocardial mitochondrial function [34] and restore ATP [29] after CA. Therefore, our data suggest that preservation of mitochondrial function during CA may be an important mechanism underlying the beneficial effects of CPR. The effect of CPR on preserving mitochondrial function and subsequently the energy metabolism has potential clinical implication. It suggests that in addition to high quality CPR, additional intervention aiming at preserving mitochondrial function and rapid reductions of cerebral metabolism during CA, such as intra-arrest hypothermia and pharmacologically induced cerebral hibernation, may be the new strategies for neurological protection in CA and CPR.

Our study has several limitations. We focused on the early changes of brain mitochondrial function and high-energy phosphates after CA. Thus, our study was limited by the absence of outcome data regarding the mitochondrial,

morphological, and functional changes after ROSC due to the current experimental design. Additional investigation is needed to elucidate if preserved intra-arrest mitochondrial function could be translated into improved cerebral function following successful resuscitation. Moreover, our findings should be more carefully interpreted when applied to clinical practice because of the more complex clinical conditions and the limitations of current animal model.

We conclude that CA causes cerebral mitochondrial dysfunction along with decay of high-energy phosphates, which could be mitigated with the intervention of high quality CPR. This may broaden our understanding of the underlying pathophysiological processes involved in cerebral ischemic injury and provide a new option for cerebral preservation during the global cerebral ischemia of CA.

Abbreviations

ATP: Adenosine triphosphate
ADP: Adenosine diphosphate
CA: Cardiac arrest
CPR: Cardiopulmonary resuscitation
HPLC: High-performance liquid chromatography
MAP: Mean aortic pressure
PCr: Phosphocreatine
RCR: Respiratory control ratio
ROSC: Return of spontaneous circulation
VF: Ventricular fibrillation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Jun Jiang and Xiangshao Fang contributed equally to this study.

Acknowledgments

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Research Article

Towards the Automated Analysis and Database Development of Defibrillator Data from Cardiac Arrest

Trygve Eftestøl[1] and Lawrence D. Sherman[2,3]

[1] *Department of Electrical and Computer Engineering, Faculty of Science and Technology, University of Stavanger, 4036 Stavanger, Norway*
[2] *Department of Medicine, University of Washington, 999 3rd Avenue, Suite 700, Seattle, WA 98104, USA*
[3] *Department of Bioengineering, University of Washington, 999 3rd Avenue, Suite 700, Seattle, WA 98104, USA*

Correspondence should be addressed to Trygve Eftestøl; trygve.eftestol@uis.no

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Background. During resuscitation of cardiac arrest victims a variety of information in electronic format is recorded as part of the documentation of the patient care contact and in order to be provided for case review for quality improvement. Such review requires considerable effort and resources. There is also the problem of interobserver effects. *Objective.* We show that it is possible to efficiently analyze resuscitation episodes automatically using a minimal set of the available information. *Methods and Results.* A minimal set of variables is defined which describe therapeutic events (compression sequences and defibrillations) and corresponding patient response events (annotated rhythm transitions). From this a state sequence representation of the resuscitation episode is constructed and an algorithm is developed for reasoning with this representation and extract review variables automatically. As a case study, the method is applied to the data abstraction process used in the King County EMS. The automatically generated variables are compared to the original ones with accuracies $\geq 90\%$ for 18 variables and $\geq 85\%$ for the remaining four variables. *Conclusions.* It is possible to use the information present in the CPR process data recorded by the AED along with rhythm and chest compression annotations to automate the episode review.

1. Introduction

During resuscitation of cardiac arrest victims automated external defibrillators (AEDs) record a variety of information in electronic format. In many emergency medical service (EMS) systems this electronic information is downloaded to a computer system as part of the documentation of the patient care contact and in order to be provided for review of the case for quality improvement activities. The electronic information will then be available as digital files which include physiological signals and also operational data related to the defibrillator (energy delivered, mode: automatic or manual, impedance, time of each event, etc.) logged from the defibrillator. Data related to operation of the defibrillator we denote as "CPR process data." This data may be organized and stored in a registry of the cardiac arrest cases. This registry may then serve as a database that may be used in studies of resuscitation strategies directed at improving survival from cardiac arrest. The collected physiological data includes the electrocardiogram recording the cardiac activity of the patient and depending on the recording features of the device, the impedance between electrodes, the acceleration and force of chest compressions, end tidal CO_2, blood pressure, and possibly other biometric measures. The CPR process data defined above also carries essential information about critical time points such as the exact time the device is turned on, the results of each shock advisory analysis, and the precise time of defibrillation shocks. In addition to the CPR process data that the device may produce, there are various written or electronically generated reports documenting the resuscitation episode along with clinical and demographic information. These reports are filed by dispatching centers and by the EMS responders during and following the resuscitation. In many systems an audio recording is made allowing a listener to review the course of resuscitation to supplement the ECG presentation and written reports.

It is our belief that the integration of CPR process data combined with an automatic analysis of the physiologic signals would make it possible to objectively and efficiently analyze resuscitation episodes in an objective reproducible format. Such analysis is important as it provides the means for analyzing and archiving parameters describing the quality of cardiopulmonary resuscitation (CPR). A simple example is the ratio of hands off intervals (HOI) during therapy. In several studies both ECG and chest compression tracings have been reviewed to accurately identify all such HOI. These studies have shown that, despite the subjective impression by rescuers that CPR delivery was adequate, in fact the HOI duration exceeded the recommendations given in the resuscitation guidelines [1, 2]. These findings had a significant impact on the 2005 guidelines revision [3]. As a result, an increased focus and attention to continuous uninterrupted chest compressions has had a positive effect on survival rates as reported in several studies [4–7]. For these studies to give significant results, quite a large number of resuscitation episodes were collected and reviewed. This involved considerable effort for the reviewers and careful definitions of the parameters to be recorded in order to make the resulting analysis objective and relevant. Interobserver variation is a significant confounding factor in these studies. The interpretation often involves determining the cardiac rhythm and the transitions between rhythms both with and without the presence of chest compressions. These rhythm and chest compression annotations involve interpretation of the ECG for rhythm assessment and of the compression signals for identifying chest compression sequences.

The present study is undertaken in order to determine whether it is feasible to automate the process of data analysis and extraction of the clinically relevant features. In particular we seek to demonstrate that information which is currently collected by manual review of cases of ventricular fibrillation cardiac arrest involving many hours of review can be replicated using an automated extraction technique. This will be done through the following three steps: (1) The concept of a minimal information set defined by important events during the resuscitation is proposed. (2) From the minimal information set a state sequence model is constructed. (3) Algorithms are designed to reason over the state sequence model to automatically replicate the manual interpretation of CPR process data.

2. Methods

There are several layers of information involved in the interpretation of a resuscitation episode. Some of the clinical variables are derived directly from the CPR process data and annotations of rhythm and therapeutic events and are therefore fundamental or primary. Other variables, the secondary variables, can be inferred or calculated from the primary variables. From these primary information variables we furthermore propose a state sequence model from which it will be possible to design algorithms to perform the reasoning to infer the secondary variables.

2.1. Defining the Primary Information Objects. In developing the automation of such a process it was necessary to consider the type of information to be retrieved. Some objects of information are more fundamental than others. One may distinguish a hierarchy of these objects as primary and secondary in the sense that the secondary objects may be determined from the information present in the primary objects. Our hypothesis is that the secondary objects of information can be derived automatically from the primary objects by designing an algorithm that reasons on the primary objects to produce the secondary objects. It is our hypothesis that these primary objects include a subset of the elements in the AED event record and of the annotations of rhythm transitions and of the start and stop times of the chest compression sequences.

To formalise this concept, we associate these primary information objects to categories of important events during a resuscitation episode. A resuscitation episode can be described as an episode starting at time t_s and ending at t_e. Throughout the episode, there are important events e_i that can be associated with a given time t_i. In our model of resuscitation, we define two important categories of events: *therapeutic* and *rhythmic* events. (We will also refer to rhythmic events and states as response events and states.) The therapeutic events are limited to the set $T_e = \{c1, c2, d1, d2\}$ marking the start and end of a compression sequence (c1 and c2) and start and end of a defibrillation (d1 and d2).

The rhythmic events represent rhythm transitions which we limit to the set $R_e = \{vf, vt, as, pe, pr\}$ marking transitions into ventricular fibrillation (vf), ventricular tachycardia (vt), asystole (as), pulseless electrical activity (pe), and pulse giving rhythm (pr).

Examples of both types of annotations are shown at the top and bottom inside each plot window of the tracings of the AED signals in Figure 1 where CPR process data and annotations are shown for three different types of AEDs.

The first step in the automated review process will be to collect these events or primary information objects which we denote as PIOs from the manually recorded data and from the defibrillator. These PIOs will be processed to construct the state sequence which we denote as the "Representation of the Resuscitation Event" (RORE). The RORE (to be discussed in more detail below) is then input to the reasoning algorithm which produces the secondary information objects (denoted as SIO). The derived database can then be compared to the original database to determine the accuracy and validity of using only the PIOs to determine and define all of the information present in the database. This serves the twofold purpose of defining the minimal dataset (PIOs) which needs to be collected by an automatic algorithm designed for this purpose and also tests the ability of the RORE created only from the PIO to serve as the sole source for an accurate clinical database to be used in resuscitation research and quality improvement activities.

2.2. Using Primary Information Objects to Create Representations of Resuscitation Episodes. In a previous article Eftestøl et al. presented a conceptual framework for representing the

data from resuscitation episodes [8]. This representation is essentially a standardized data format developed to describe a resuscitation episode. Briefly, the RORE involves two aspects that are separately modeled, the therapy domain state sequence and the response (or rhythmic) domain state sequence. Generally, we denote a resuscitation episode as a sequence of changing states. The individual states are defined initially within either the therapy or the response domain and these two aspects are put together in a combined sequence to concisely describe the resuscitation. A change in either domain constitutes a change in the state of the combined episode representation. The transitions between the states in each domain are represented as delimited time intervals, where the start and end time for each interval is given for that state. The start and end times therefore indicate the time of transition into and out of the represented state. The time of transition out of a specific state corresponds to the time of transition into the next state. For the response domain, the states are the various cardiac rhythms that occur throughout a resuscitation episode. In the therapy domain, the states are the interventional treatments given to the patient: in this study these were the chest compression sequences, hands off intervals, and defibrillation shocks. These two sequences or representations and the combination of these two domains constitutes the RORE.

A Formalised Description of the Concept in the Context of the PIO Events. To be able to design algorithms that can reason on the information we need a model that captures the relationship between the elements both in terms of the course of time and type of event.

To each type of event e_i, there is the time point t_i describing the transition or onset time. One can say that the event marks a change of state, the state E_i determined by the type of event at time t_i. The state is unchanged until the next event e_{i+1} marks the transition into the next state E_{i+1}.

To each state, we define the corresponding time interval, $T_i = [t_i, t_{i+1}]$. Thus, the course of events during a resuscitation episode will be defined as a continuous sequence of states $S = \{(T_1, E_1), (T_2, E_2), \ldots, (T_N, E_N)\}$ where the time intervals are ordered according to time since start of episode, t_s.

We define three sets of states. The first two sets are related to the therapeutic and rhythmic events. The therapeutic states are limited to the set $S_e = \{\mathrm{C}, \mathrm{H}, \mathrm{D}\}$ marking the compression sequences (C), the hands-off intervals (H), and the defibrillations (D). The rhythmic states are limited to the set $S_r = \{\mathrm{VF}, \mathrm{VT}, \mathrm{AS}, \mathrm{PE}, \mathrm{PR}\}$ which represents ongoing rhythms the start and end of which are defined by the corresponding transition events. VF is the state ongoing in the time interval the start of which is marked by the transition event vf and ended by one of the other transition events in R_e. The relationship between the other rhythmic events as, vt, pe, and pr and states AS, VT, PE, and PR is similar. The third set is constructed from the combination of the therapeutic and rhythmic states in the time interval where the two types of states are unchanged. If the rhythmic state sequence is

$$S_R = \{([t_0, t_3], E_{R1}), ([t_3, t_4], E_{R2})\} \quad (1)$$

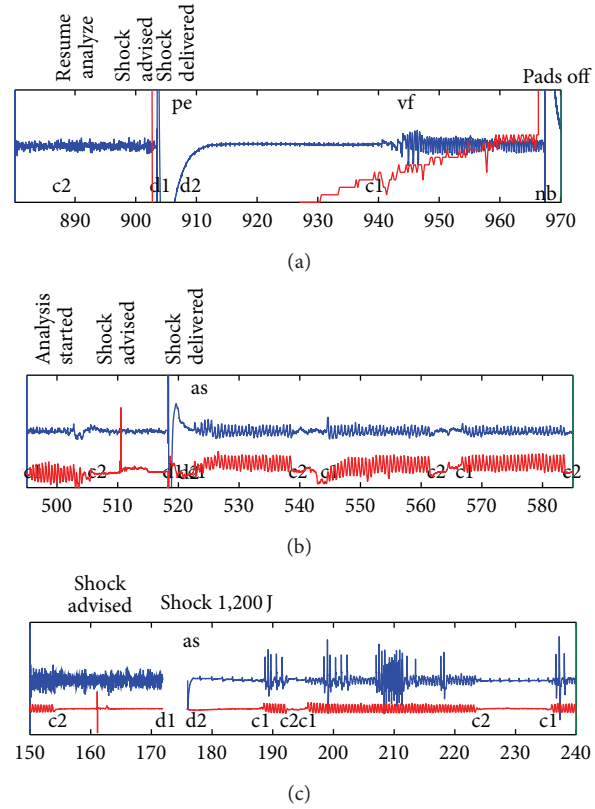

Figure 1: Signals and data recorded by three different automated external defibrillators: (a) Philips Forerunner 2, (b) Philips MRx, and (c) Physiocontrol Lifepak 12. The blue and red tracings show the electrocardiogram and thoracic impedance, respectively. Examples of information recorded in the defibrillator's electronic log are shown above each plot window. Annotations of rhythm transitions and therapeutic events are shown at the top and bottom inside each plot window.

and the corresponding therapeutic state sequence is

$$S_T = \{([t_0, t_1], E_{T1}), ([t_1, t_2], E_{T2}), ([t_2, t_4], E_{T3})\}, \quad (2)$$

the combined state sequence will be

$$S_C = \{([t_0, t_1], E_{T1}E_{R1}), ([t_1, t_2], E_{T2}E_{R1}), ([t_2, t_3], E_{T3}E_{R1}), ([t_3, t_4], E_{T3}E_{R2})\}. \quad (3)$$

Note how the state labels from S_R and S_C are concatenated.

For the tracing in Figure 1(a), the three state sequences representing the part of the resuscitation episode that is shown will be as follows:

$$S_T = \{([740.8, 805.2], \mathrm{H}), ([805.2, 887.2], \mathrm{C}), ([887.2, 903.3], \mathrm{H}), ([903.3, 908.3], \mathrm{D}), ([908.3, 938.8], \mathrm{H}), ([938.8, 1062.0], \mathrm{C})\}, \quad (4)$$

$$S_R = \{([793.6, 908.3], \mathrm{VF}), ([908.3, 944.0], \mathrm{PE}), ([944.0, 1062.0], \mathrm{VF})\},$$

and the combined sequence will be

$$S_C = \{([793.6, 805.2], \text{HVF}), ([805.2, 887.2], \text{CVF}), ([887.2, 903.3], \text{HVF}), ([903.3, 908.3], \text{DVF}), ([908.3, 938.8], \text{HPE}), ([938.8, 944.0], \text{CPE}), ([944.0, 1062.0], \text{CVF})\}. \quad (5)$$

2.3. Designing Algorithms Reasoning on the RORE. The RORE is well suited for designing reasoning algorithms which aims to mimic the interpretation a clinician will do. The basic principle is that the algorithms can identify time intervals in the state sequences fulfilling criteria expressed by the state sequence labels. For example, in the current study, the RORE was implemented in MATLAB where the state sequences can be realised as a list with the sequence labels. The time intervals are placed in corresponding lists so that, if a specific state symbol is found in position i in the list of state sequence labels, the corresponding time interval can be found in position i in the list of state sequence time intervals. The complete episode from which the tracing in Figure 1(a) originates is represented by the therapy sequence S_T = {H, D, H, C, H, D, H, C, H, C, H, C, H, C, H, C}, the rhythm sequence S_R = {VF, PE, VF, PE, VF, PE, VT, VF, PE, VF, UN}, and the combined sequence S_C = {HVF, DVF, HPE, CPE, CVF, HVF, DVF, HPE, CPE, CVF, CPE, HPE, CPE, HPE, HVT, HVF, CVF, HVF, CVF, HPE, CPE, CVF, CUN}. (Notice the use of UN for unknown state.) The framework is quite flexible where the RORE serves as the vocabulary on which it is possible to reason to derive the SIOs. For example, the initial rhythm can be determined by retrieving the first element from SR. The time of the defibrillations can be determined by searching ST for occurrences of D and retrieving the corresponding time intervals.

As we will see later, the review will be focused on the pre- and postshock periods of each shock. This can be done by repeating the analysis for each shock, wherein the state sequences between the current and previous shock (or beginning of episode) are extracted to represent the preshock period. The states between the current and next shock (or end of episode) are extracted to represent the postshock period. Subsequently, the start of the first compression sequence and the end of the last compression sequence can be found by searching the preshock therapy sequence for the first and last occurrences of C. The duration of the preshock compression sequence can furthermore be by subtracting the start time for the time interval of the first C from the end time of the last C.

We will use this kind of reasoning to illustrate how this methodology can be used in the following case study.

3. A Case Study

The extraction from the King County database utilized in the current study will act as a model for the design of automatic data collection algorithms which is the goal of this study. By using this manually acquired data, a particular representation of the cardiac arrest for each subject will be developed which will contain the candidate set of variables to exactly describe and document the resuscitation episode. These automatically derived variables will be a replica of the original variables and the two data sets will be compared for evaluation.

3.1. Current State of the Art. The EMS division of King County has registered all sudden cardiac arrests treated in a large metropolitan area surrounding Seattle, WA, since 1976 [6, 9, 10]. This database has been used in several retrospective studies, where the study objectives have been diverse. Specific examples include the recording of Utstein elements to investigate long term survival among resuscitated patients [9], the effect of time to EMS arrival on survival [10], and the effect of resuscitation algorithm changes on survival [11], and the application of public access defibrillation affects EMS therapy [12]. In the scope of the present investigation, studies using the information derived from interpretation of the CPR in association with the analysis of the physiologic signal are of particular relevance. For example, in one study the effect of a change in the cardiac arrest protocol introduced to decrease the hands off interval (HOI) associated with shock delivery was assessed [6]. The effect of the protocol change was evaluated by analyzing time intervals before and after shocks. In another study designed to develop a method to predict the outcome of defibrillation, ECG waveforms prior to the first shock were extracted for analysis along with information regarding whether ROSC occurred following the defibrillatory shock [13]. For all of these studies, the abstraction of information was carried out by following a carefully scripted case review routine. This abstraction process includes review of the EMS medical incident report forms using specifically designed forms based on Utstein variables, review of electronic recordings from the AEDs, again using well-defined criteria, and using predefined time points for rhythm assessment. In addition there was direct audio review of dispatch recordings for each case. These records are reviewed to determine various aspects of therapy, such as duration and frequency of chest compressions, number and timing of defibrillations, response to shocks, and the presence and duration of HOI. In King County the review process is clearly defined in a data dictionary where each variable generated from the review is listed with an explanatory description and the possible values it can have. After the review, the variables are stored in an Access database (Microsoft Corporation). The review itself is conducted by dedicated staff members who receive extensive training in abstraction techniques prior to performing independent reviews. All cases are abstracted by a minimum of two reviewers. All cases with conflicts are adjudicated by a supervising physician expert in ECG analysis.

3.2. Overview of Data Collection. The total data set consisted of a convenience sample of 75 cardiac arrests from the King County registry which were completely deidentified using custom software written for this purpose. The study was approved by the IRB of the University of Washington. The study was divided into two phases. In the development phase, 20 cases were randomly selected and used to create

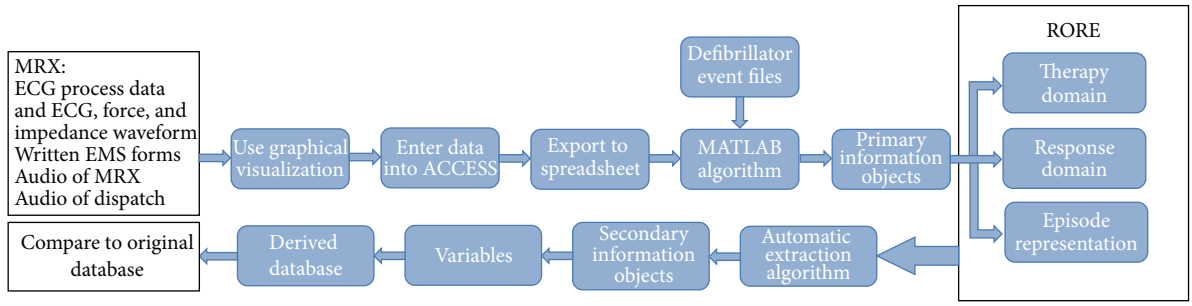

Figure 2: The process of deriving the variables from the manual review; the generation of the representations used for the further algorithmic reasoning for deriving the variables automatically.

the algorithm which utilized the two sources of clinical information available. The algorithm used both the raw data from the original database which had been placed in Excel formatted files and the CPR process data (from the defibrillator downloads of the defibrillator data files) to create the summary of the case termed the "Representation Of the Resuscitation Episode" (RORE). Then this process was reversed so that the RORE was used to recreate a second database whose purpose was to determine if the original data could be accurately abstracted from the RORE to recreate the clinical record in an automatic algorithmically driven manner. After the method had been adjusted to perform well on the development set data, its accuracy was then tested on a validation set of the remaining 55 cases from the database (Figure 2).

3.3. Overview of the Variables to be Replicated. To begin the process, data fields of interest were extracted from storage in the King County EMS repository which is an Access database by being exported to an Excel spreadsheet. The patient population was restricted to those treated with MRx AED devices (Philips Inc.) which uses a small "puck" placed under the rescuers hands during chest compressions to very accurately record the force and acceleration used in chest compressions. The CPR process data consisted of the electronic files stored by the MRx during each resuscitation episode. The electronic data were downloaded to computer archives immediately after the episode. The written report of the patient care encounter as filed by the EMS crew following the resuscitation was also used in the manual abstraction process.

There are several types of variables in the database. Variables describing the defibrillation shocks, chest compressions, and patient response were included. Each of these general categories of variables contain subsections which detail the time of each event, the operation of the device (i.e., Joules delivered with each shock, impedance at each shock, etc.), and variables describing transitions in rhythm related to the patient's response after each shock. Each row in the Excel spreadsheet stores the variables related to one specific shock and includes the following.

(1) Time Events. Each time event is given by three variables, hour, minute, and second of the day. For example, "ECG start time" corresponding to the AED power on time is registered in the three variables: ecghr, ecgmn, and ecgsc. Each of these is coded numerically: 0–23 for hour, 0–59 for minutes and seconds. We will refer to these collectively as ecgtime (hr:mn:sc) denoted by the variable name "ecgtm." The other time data points reported for a shock include the events describing therapy prior to and including the shock: "First compression time," "Last compression time," and "Shock time" (variable names "fctm," "lctm," and "shktm"). The time events following a shock describe the patient's response and give the time points for transitions to specific rhythms after each shock is given: "VF onset time" and "ROSC time" (return of spontaneous circulation) (variable names "vfonsettm" and "rsctm"). Table 1 shows a more detailed view of the time event variables.

(2) Device Operation and Therapy. "Shock number," "Number of shock sequences recorded," and "Number of shocks in sequence" record the shock sequence number, the number of electrical shocks delivered to the patient, and the number of "stacked" shocks without intervening CPR (variable names "shkn," "ssrecord," and "shks"). The AED operating mode, either "manual" or "advisory," was coded in the variable "mode." EMS provision of CPR was coded in the variable "CPR." The energy and impedance of the shock are given by the variables "enrgy" and "imp," respectively. Table 2 shows a more detailed view of the device operation and therapy variables.

(3) Patient's Response Following a Shock. For the initial rhythm, the variable "init_rhy" describing the rhythm at the start of the ECG recording was captured. The rhythms at 10, 30, 60, and 120 seconds after the shock were recorded in the variables "r10," "r30," "r60," and "r120." These time points were originally developed in an effort to determine the outcome of the defibrillatory shock as precisely as possible. It was felt that the first 2 minutes after shock were most important in determining if a shock had been successful in producing an organized and possibly perfusing rhythm and that, by using discrete, well-defined points, the rhythm changes could be determined in a time window of relevance to evaluating the effect of resuscitation therapies. In addition, the variable "orgpr" is used to describe whether there was an organized rhythm at any time during the interval before the next shock (or the end of the recording if no more shocks were given). In a similar manner "vfpr" indicates whether there is

Table 1: The time variables with descriptive names, variable names, coding, and explanation of each variable.

	Variable in Access database	Possible values	Description
ECG start time	ecghr	(0–23, 99) 99 = unknown	The hour of actual start time of the ECG
ECG start time	ecgmn	(0–59, 99) 99 = unknown	The minute of the actual start time of the ECG
ECG start time	ecgsc	(0–59, 99) 99 = unknown	The second of the actual start time of the ECG
First compression time	fchr	(0–23, 88, 99) 88 = no CPR administered, 99 = unknown	Hour of first compression, prior to shock. *Record only if first compression on record is actually the first compression given*
First compression time	fcmn	(0–59, 88, 99) 88 = no CPR administered, 99 = unknown	Minute of first compression, prior to shock. *Record only if first compression on record is actually the first compression given*
First compression time	fcsc	(0–59, 88, 99) 88 = no CPR administered, 99 = unknown	Second of first compression, prior to shock. *Record only if first compression on record is actually the first compression given*
Last compression time	lchr	(0–23, 88, 99) 88 = no CPR administered, 99 = unknown	Hour of last compression before shock
Last compression time	lcmn	(0–59, 88, 99) 88 = no CPR administered, 99 = unknown	Minute of last compression before shock
Last compression time	lcsc	(0–59, 88, 99) 88 = no CPR administered, 99 = unknown	Second of last compression before shock
Shock time	shkhr	(0–23, 99) 99 = unknown	Actual hour of shock delivery
Shock time	shkmn	(0–59, 99) 99 = unknown	Actual minute of shock delivery
Shock time	shksc	(0–59, 99) 99 = unknown	Actual second of shock delivery
VF onset time	vfonsethr	(0–23, 99) 99 = no onset, patient remained in VF blank indicates no vf	Hour of VF onset, best estimate when underneath CPR artifact
VF onset time	vfonsetmm	(0–59, 99) 99 = no onset, patient remained in VF blank indicates no vf	Minute of VF onset, best estimate when underneath CPR artifact
VF onset time	vfonsetss	(0–59, 99) 99 = no onset, patient remained in VF blank indicates no vf	Second of VF onset, best estimate when underneath CPR artifact *Therefore a 99 : 99 : 99 indicates an unsuccessful defibrillation*
ROSC time	rschr	(0–23, 99) 99 = unknown	Actual hour of ROSC
ROSC time	rscmn	(0–59, 99) 99 = unknown	Actual minute of ROSC
ROSC time	rscsc	(0–59, 99) 99 = unknown	Actual second of ROSC

a recurrence of VF prior to the next shock. Table 3 shows a more detailed view of the patient's response variables.

Primary and Secondary Information Objects. Table 4 provides an overview of the primary information objects that we use to construct the RORE. Considering the variables registered during the manual review, some of these basically reflect the same information as the primary information objects, while the remaining variables correspond to secondary information objects. Table 5 provides an overview of all the variables handled in this study. Variables are categorized as describing time events, patient response, and device operations and therapy and primary and secondary information objects are indicated by the acronyms PIO and SIO, respectively.

3.4. Generating the Representations. To generate the RORE, the information recorded by the defibrillator and contained in the CPR process data on the device is used directly for the time and shock data: that is, the time the device is turned

Table 2: The variables describing device operation and therapy with descriptive names, variable names, coding, and explanation of each variable.

	Variable in Access database	Possible values	Description
Shock number	shkn	≥0 and <21	Shock sequence number.
Number of shock sequences recorded	ssrecord	(>0 and <31) or 99 99 = unknown	This describes the number of electrical shocks delivered to the patient as recorded on the AED total shocks received by the patient.
Number of shocks in sequence	shks	1–31	The number of shocks without intervening CPR. For example, 1 = no stacked shocks while > 1 = stacked shocks. After 2005 no case should have stacked shock.
Mode	mode	1 = manual 2 = semiautomatic & advisory 9 = unknown	This is the mode of the AED at the time of the shock
EMS CPR prior to shock?	cpr	1 = yes 2 = no 9 = unknown	Description of if EMS CPR was administered to patient before shock was delivered.
Impedance at 1st shock	imp	Measured in Ohms	Impedence at time of first shock sequence (50–200, 999) 999 = unknown.
Energy of 1st shock	enrgy	Measured in Joules	Energy of first shock in sequence.

on, the exact time of each shock, number of joules delivered, impedance at time of shock, and so forth are obtained directly from the device event files. In addition, the information for rhythms and chest compressions extracted by manual review of the ECG using Event Review 3.1 is then recorded in the ACCESS database and subsequently placed in the Excel spreadsheet (Figure 2). Several PIOs are extracted from both the written EMS reports and from the manual review. We have observed and wish to stress that, in order to accurately describe the rhythm data, the only data points required are the times of rhythm transitions between different rhythm types. This decreases the amount of information stored in the RORE substantially. This is clearly illustrated in the following example (see Figure 3).

In this resuscitation we are viewing the ECG (blue) and the thoracic impedance (red). The ECG represents the cardiac activity while the impedance indicates the chest compressions. The time interval shown here is from 180 seconds to 330 seconds. This shows a section of VF beginning at 180 seconds with no CPR being performed and during which analysis of the ECG has recommended a shock. The shock is delivered at 198 seconds (d1) and CPR begins at 201 seconds. The CPR artifact shows a possible QRS complex at 204 seconds and a definite QRS at 221 seconds and again at 229 seconds. In the database used for this study the rhythm was recorded at predetermined time points (10, 30, 60, and 120 seconds). An organized rhythm was defined as being at least 2 beats within the 5 seconds before and after the time point. Since the 30-second time point is 228 seconds this does not qualify as an organized rhythm yet. At 60 seconds (258 sec.) an organized rhythm is present without a pulse being detected. VF then recurs at 282 seconds and persists with CPR artifact until the end of the trace. One can easily appreciate that the description of this 150-second period of resuscitation is complete but quite lengthy. To condense the description for the KCEMS database we attempted to reduce the record by focusing on specific time points immediately after the shock. This is recorded in the database as described above with the rhythm at each time point recorded. Because discrete predetermined time points are used there is an inherent inaccuracy in the record. The rhythm transition points are only estimated by the time points used and then only if the transition occurs within the first two minutes after shock. In contrast, for the PIO based data recorded in the response domain, only the transitions in rhythm are recorded and these would ideally be recorded at the precise time of occurrence. The episode in the lengthy description above is shown in RORE format in Figure 4. For the 180 to 330 time interval there are 5 lines of notation in the therapy domain, 4 lines in the response domain, and 8 lines in the overall episode representation (Figure 4 outlined portion). Ideally, the rhythm transitions would be determined exactly by direct manual review or by an automatic computer algorithm with an overread by a reviewer. This would provide the exact times of transition. In this study, to determine "proof of concept," the KCEMS database was used to derive the time points of transitions, while recognizing that they would be only estimates of these transitions. Using the KCEMS database the response domain is formed as follows. The events in the database are recorded in seconds so that the initial rhythm of VF is noted to begin at 46 seconds after the defibrillator is turned on at which time the leads are connected. The next rhythm transition is to asystole at 208 seconds (r10, 10 seconds after the shock) followed by transition to an organized rhythm without a pulse at 258 seconds (r60, 60 seconds after the shock) and a return to VF at 283 seconds. Note that the reoccurrence of VF was identified as accurately as possible by the reviewers while the organized rhythms were recorded only at the 4 time points. The response domain for these events is shown in seconds as "46–208: VF" and then "208–258: AS" to indicate asystole

Table 3: The response variables with descriptive names, variable names, coding, and explanation of each variable.

	Variable in Access database	Possible values	Description
Initial rhythm	init_rhy	1 = asystole, 2 = VF, 3 = pulseless VT, 4 = organized, 5 = indeterminate (VF/organized), 6 = indeterminate (VF/asystole), 7 = indeterminate (brady), 8 = indeterminate, 9 = unknown	Description of what the initial rhythm recorded was as determined from the AED. Codes in parenthesis refer to indeterminate between the two stated rhythms. If initial rhythm NOT VF and patient subsequently fibrillates, record original VF onset time, for substudy of secondary VF.
Preshock rhythm	rhyb4	1 = asystole, 2 = vf, 3 = vt, 4 = org, 5 = indeterm-(vf/org), 6 = indeterm-(vf/asys), 7 = indeterm-brady, 8 = indeterm, 9 = unknown	Description of what the preshock rhythm recorded was. Codes in parenthesis refer to indeterminate between the two stated rhythms.
Rhythm 10 secs after the last shock	r10	1 = asystole, 2 = vf, 3 = vt, 4 = org, 5 = indeterm-(vf/org), 6 = indeterm-(vf/asys), 7 = indeterm-brady, 8 = indeterm, 9 = unknown	Description of what rhythm recorded 10 seconds after the shock was. Codes in parenthesis refer to indeterminate between the two stated rhythms. Use discretion to take the rhythm ±5 seconds from 10 seconds after shock.
Rhythm 30 secs after the last shock	r30	1 = asystole, 2 = vf, 3 = vt, 4 = org, 5 = indeterm-(vf/org), 6 = indeterm-(vf/asys), 7 = indeterm-brady, 8 = indeterm, 9 = unknown	Description of what rhythm recorded 30 seconds after the shock was. Codes in parenthesis refer to indeterminate between the two stated rhythms. Use discretion to take the rhythm ±5 seconds from 30 seconds after shock.
Rhythm 60 secs after the last shock	r60	1 = asystole, 2 = vf, 3 = vt, 4 = org, 5 = indeterm-(vf/org), 6 = indeterm-(vf/asys), 7 = indeterm-brady, 8 = indeterm, 9 = unknown	Description of what rhythm recorded 60 seconds after the shock was. Codes in parenthesis refer to indeterminate between the two stated rhythms Use discretion to take the rhythm ±5 seconds from 60 seconds after shock.
Rhythm 120 sec after the last shock	r120	1 = asystole, 2 = vf, 3 = vt, 4 = org, 5 = indeterm-(vf/org), 6 = indeterm-(vf/asys), 7 = indeterm-brady, 8 = indeterm, 9 = unknown	Description of what rhythm recorded 120 seconds after the shock was. Codes in parenthesis refer to indeterminate between the two stated rhythms. Use discretion to take the rhythm ±5 seconds from 120 seconds after shock.
VF prior to next shock?	vfpr	1 = yes, 2 = no, and 9 = unknown	Description of whether or not there was VF between shocks, or between the last shock and the end of this recording as determined from audio or the MRIF. Not to capture VF at any time after device turned off.

Table 3: Continued.

	Variable in Access database	Possible values	Description
Organized rhythm prior to next shock?	orgpr	1 = yes, 2 = no, and 9 = unknown	Description of whether or not there was an organized rhythm between shocks, or between the last shock and the end of the recording. Best organized rhythm (wide/narrow, and rate) will be taken within 3 minutes of the final shock on recording.
ROSC	rosc	1 = yes, 2 = no, and 9 = unknown	Description of whether return of spontaneous circulation occurred.

Table 4: The primary information objects (PIO). These variables constitute the primary information objects (PIO) and are used to model the entire resuscitation episode. The therapy and response domains are described independently. For each domain the entire time span of the episode is described as a sequence of interchanging states. For each state change, the corresponding transition times are given which specify the times entering and leaving the state. The entering time of a state corresponds to the leaving time of the prior state unless it is the beginning of the episode. The leaving time of a state corresponds to the entering time for the next state unless it is the end of the episode.

Transition time	Variable domain: Patient's response		Therapy	
	State	Code	State	Code
Seconds	Ventricular fibrillation	VF	Chest compressions	C
Seconds	Ventricular tachycardia	VT	Hands off interval	H
Seconds	Asystole	AS	Defibrillation	D
Seconds	Pulseless electrical activity	PE	Unknown	U
Seconds	Pulse generating rhythm	PR		
Seconds	Unknown	UN		

as the rhythm at 10 seconds after the shock. Then there is a transition to an organized rhythm without a pulse: "258–283: PE" and another transition when VF recurs: "283–343: VF." This method produces a succinct record of rhythms as shown in Figure 4.

The therapy domain states are presented in a similar manner. The chest compression times are read directly from the variables for first and last compression times prior to the each of the shocks present in the ACCESS database. All other information is read from the CPR process data as recorded in the MRX defibrillator. For example, in the defibrillator event log all events are listed along with the time in milliseconds. The time for each shock can be found by doing a search of the MRx recorded data for the text string "shock delivered" indicating the shock events. Once found, the corresponding time is given in milliseconds and is converted to seconds. This is illustrated in Figure 3 in which the defibrillator log events such as "shock delivered" can be seen outside the trace boxes. In this figure the rhythms noted in the KCEMS database have been inserted as rhythm annotations such as "vf" and "as" and are seen in the upper portion just inside the boxes. The therapy related annotations shown at the bottom inside of the boxes ("c1"/"c2" and "d1"/"d2") are the start and end of compression sequences and defibrillation events respectively). The therapy domain representation was created from the KCEMS database in a manner similar to that described above for the response domain. For the 180–330-second period shown in Figure 3 there is a hands off interval from the start at 180 seconds to the time of the shock at 196 seconds. After the shock follows a brief hands off interval continuing until compressions start at 200 seconds which continues with brief pauses for ventilations until chest compressions are halted at 322 seconds. Lines 3–7 in the therapy domain (Figure 4) represent this period of the resuscitation. The RORE is easily constructed by combining the therapy and response representations and gives a comprehensive picture of the relationship between the provided therapy and the patient response to the treatment. In the following, the therapy domain, response domain, and the RORE make up the completed representation using the PIOs as described above.

3.5. Reasoning from the Representation Back to Create the Derived Data. The working principles of the reasoning algorithms are described in the following. For increased readability a prose form has been chosen rather than using a pseudocode description. All the algorithms have been implemented and run in MATLAB.

Before beginning to work back from the representations to the database it is necessary to establish the precise absolute time for the resuscitation. The KCEMS database uses the absolute times at the data points as extracted by manual review of the record. The times in the defibrillator log file and subsequently the representation are relative or elapsed times. In order to be able to calculate back to the absolute time used in the manual registration it was necessary to use the time as

Table 5: The variables in the original database which will be automatically replicated. The table is organized in columns to highlight the type of information the variables provide: time events, patient's response, and device operation and therapy. Each variable is labeled according to it being a primary information object (PIO) or secondary information object (SIO). All the variables labeled as PIO can also be found in the table listing the PIO variables (Table 4). The remaining variables labeled as SIO can be automatically derived from the PIO variables (listed in table PIO) by designing proper reasoning algorithms.

Variable domain					
Time events		Patient's response		Device operation and therapy	
First compression time	PIO	Initial rhythm	SIO	Shock number	SIO
Last compression time	PIO	Preshock rhythm	SIO	Number of shock seq. recorded	SIO
VF onset time	PIO	Rhythm 10 sec after last shock	SIO	Number of shocks in sequence	SIO
ROSC time	PIO	Rhythm 30 sec after last shock	SIO	Mode	SIO
Shock time	PIO	Rhythm 60 sec after last shock	SIO	EMS CPR prior to shock?	SIO
		Rhythm 120 sec after last shock	SIO	Impedance at 1st shock	SIO
ECG start time	SIO	VF prior to next shock?	SIO	Energy of 1st shock	SIO
		Org. rhythm prior to next shock?	SIO		
		ROSC	SIO		

recorded in the stored defibrillator files at the time the device was turned on as the reference time for all events. Doing this involved calculations to convert the start time from the conventional time in year/month/day/hour/minute/second format to a "serial date number" time (the number of days from January 1, 0000) used by the algorithm. These times are then converted to elapsed times for the representations. The elapsed times are then converted back to absolute times via the "serial date number" time for comparison to the original times in the database. The comparison of the times from the representations to the database can therefore be viewed as a comparison of the accuracy of the manual method of extraction by the reviewer to the automated method based on the defibrillator's internal files. In the automated method the exact time the defibrillator is turned on is used as the basis for developing the times of shocks and other events. The assumption is made that the defibrillator has been correctly synchronized with the local regional time. (See Appendix A.1 for details.)

The first primary information objects to be established and compared are the defibrillation shocks. Using the therapy domain representation, each shock in the therapy domain is identified and its position noted; the absolute time is calculated. Then the preshock and postshock periods can be identified for each shock. A preshock period is the time interval between the current shock and the previous shock and the postshock period the interval between the current shock and the next shock. If the current shock is the first shock the previous shock is replaced by the beginning of episode (BOE) marker. Likewise if it is the last shock of the recording the "next shock" is replaced by the end of episode (EOE) marker in the therapy domain. To determine the "First compression time," the preshock period of the current shock as recorded in the therapy domain is used as the time interval within which to search for the first occurrence of the symbol used to identify compressions, "C." Likewise, "Last compression time" is determined by searching the recorded preshock interval for the last occurrence of "H" which signifies a change in state from CPR to "hands off time" prior to the defibrillatory shock "D." The times for these PIOs are then converted to absolute times.

The PIOs for the rhythm domain are handled in a similar manner. Here the PIOs represent the rhythm domain states and are VF (ventricular fibrillation), AS (asystole), PE (pulseless electrical activity), PR (pulsatile rhythm), and UN (unknown). These states are represented in the RORE. Custom software was programmed to identify the preshock and postshock periods of each shock in the RORE and then to search these intervals for the first occurrence of the PIO of interest (VF onset or ROSC onset). The time associated with this event is then converted as noted above from seconds to a computer time stamp known as SDN_time (see Appendix A.1 for details) to hr:mn:sc format and is then compared to the original KCEMS database.

The next step in the conversion process from the RORE to the derived database is to derive the secondary information objects (SIOs; Table 5) from the PIOs. Determination of the Ecg_start_time and other time variables has been described with the time conversion process. The rhythm variables are handled by assuming that once a rhythm is present that it remains in that state until the notation in the RORE indicates a change in the rhythm state. The algorithm recreates the rhythm at a specific time point simply by identifying the time interval in the RORE containing this time point and noting the corresponding rhythm symbol in the RORE occurring immediately before this (for detail: Appendix A.2). To determine if there are occurrences of VF or organized rhythms before the next shock, the postshock interval is searched for occurrences of the types of rhythms in question and the results allocated to the variables "vfpr" and "orgpr."

The device operation variables are also directly related to the defibrillatory shocks. The number of each shock, "shkn," is determined by sorting the shocks in ascending order according to the sample numbers and assigning to each shock the number corresponding to its position in the ordered sequence. The number of shocks without intervening CPR is determined by initializing a counter to one. For each shock, the preshock interval is searched for compression events. If

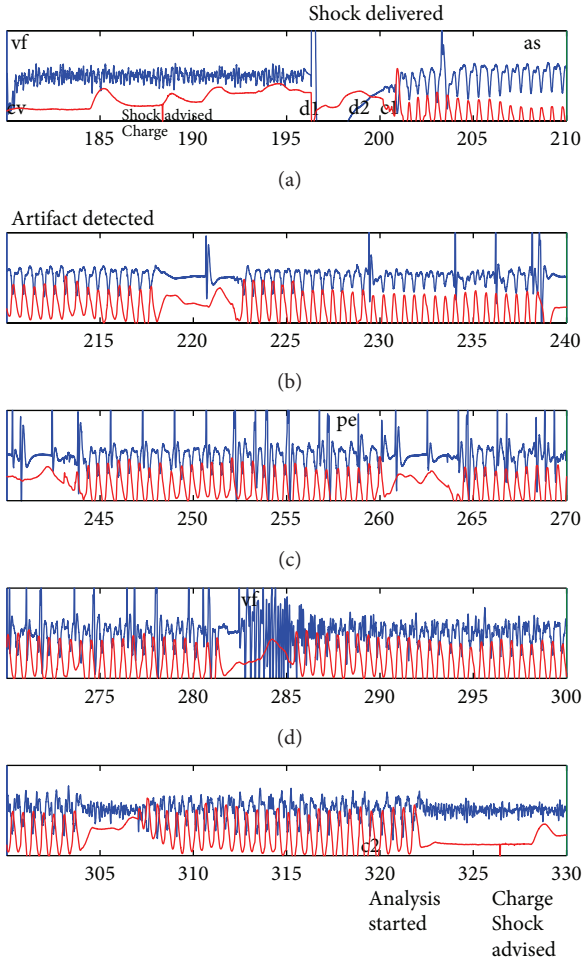

Figure 3: Case recording from MRX defibrillator. The blue tracing is the ECG. Impedance tracing is shown in red. The defibrillator log events (shock advised, charge, shock delivered, analysis started, and artifact detected), the rhythm transitions (vf: ventricular fibrillation, as: asystole, and pe: pulseless electrical activity), and annotations for start and end of compressions (c1 and c2) and defibrillations (d1 and d2) are shown. Refer to Figure 4 for the corresponding RORE representation.

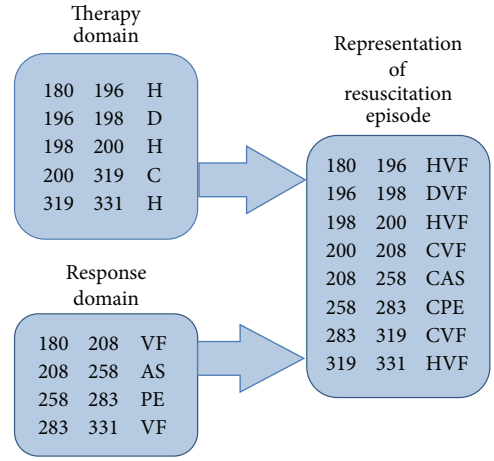

Figure 4: The representation of the resuscitation episode (RORE) including the therapy domain representation, the response domain representation, and the episode representation (for detailed explanation see Appendix C). UN = unknown, C = compressions, H = hands off chest, D = shock, CVF = compressions during VF, CAS = compressions during asystole, DVF = defibrillation for VF, PE = pulseless electrical activity, and PR = pulsatile rhythm.

none are found, the counter is incremented. The counter value is recorded in the variable "shks." The variable, "ssrec," which gives the number of recorded shocks is determined as the length of the ordered sequence of shocks. In the database, the "mode" variable indicating manual or AED mode is based on the clinical impression of the reviewer rather than on the CPR process data from the defibrillator log files. In the algorithm implementation the "modeSwitchMonitor" and "modeSwitchAED" in the defibrillator log file is used directly. Once identified for each shock the mode is compared to the database in accordance with the latest such entry prior to the time of shock. The energy and impedance variables are also manually estimated in the database by the reviewer. In contrast, in the algorithm these were read directly from the defibrillator log file in the information provided with each shock. These values are then compared.

3.6. Comparing the Original and Replicated Databases. For result evaluation, each of the automatically generated SIO variable values based on the RORE representation are compared to the corresponding manually registered values read into MATLAB from the Excel spreadsheet. These comparisons were coded according to being correct, wrong, or missing. These three categories are given the numeric codes 1, 2, and 3, respectively. The comparisons involve computing the value difference and comparing this to the specified value ranges for each of the three categories. As all values are integers, the deviations will also be integers. The value ranges are provided in the next section.

When comparing recorded event times, a deviation of 1 second or less was defined as correct, those larger than this were defined as wrong, and deviations due to the codes for persistent VF, no CPR data, and no data available were defined as "missing"(see Appendices B.1 and B.2 for details).

After tuning the system on the first twenty, it was run on the 55 episodes that had not been interpreted by the system previously. One episode was excluded as the registration was incomplete (shocks 2 and 3 missing). Error rates and a detailed analysis of the etiology of each error were performed.

4. Results

Error rates are shown in Figure 5. Rhythm annotations (a) were accurately reproduced in over 90% of cases. Discrepancies were due primarily to inconsistencies in the original database. The therapy variables showed the largest error rates in mode (15%), impedance (12%), and energy (14%)

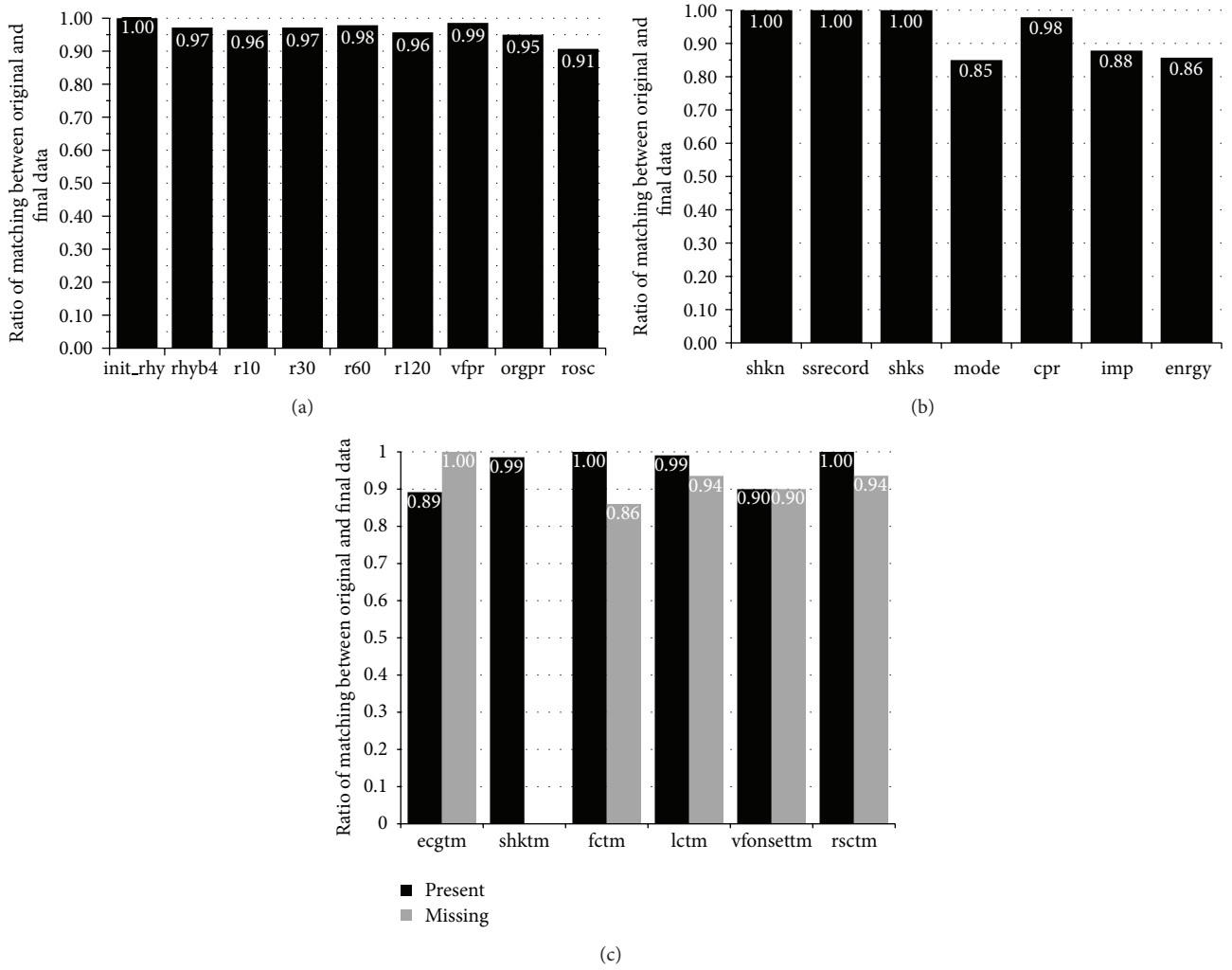

Figure 5: Summary of the match rates comparing the manually and automatically derived variable values. (a) shows match rates for rhythms at the preselected times from the database. (b) shows data regarding the defibrillator logs of shock data. (c) shows the times for ECG start, shock times, first compression and last compression times, VF onset times, and time of return of spontaneous circulation. All results are given in percentages of the ratio: correct/(correct + error). For the time variables, the lower row shows the ratio of automatically generated codes for missing values matching the manually given missing codes (gray bars).

annotations (b). Defibrillator generated data for these variables differed from estimates by the reviewers taken directly from defibrillator screen. Time variable (c) demonstrated a large number of unknown values. For those values that were present, the correlation of time values between the original database and the values recreated by the algorithm was over 90%. The missing values accounted for a large portion of values related to ECG start, first compression time, VF onset time, and time of return of spontaneous circulation. These are areas which require a judgment by the reviewer and therefore have a subjective component or may be obscured by CPR artifact or difficulty in ascertaining whether a pulse or blood pressure was present due to lack of documentation. The errors are divided between flaws in the algorithm and inconsistencies in the manual annotations.

In the following a detailed discussion is given on the various types of errors which occur.

4.1. Evaluation of the Replication of the Time Variables. The time variable results are shown in Figure 5 (for additional detail see Table 6).

For ECG start there are four errors. Three of these correspond to deviations of 4, 66, and 69 seconds and might be explained by special circumstances in the operation of the AED (see Appendix B.3 for details). One error corresponds to a deviation of more than 4 hours which we do not have an explanation for. Two of these deviations seem to propagate and might very well be the cause of corresponding deviations and reported errors for time of shock and time

Table 6: Results for the comparison between manual and automatic recording of time event variables. The table counts the number of correct, wrong, and missing values. An automatic recording is considered correct if the deviation from the manual recording is less than or equal to one second. Otherwise the recording is considered wrong. A recording is considered missing if the code 66 : 66 : 66, 88 : 88 : 88, 99 : 99 : 99 is used for either of the recordings or the manual recording was changed to 00 : 00 : 00 or 12 : 00 : 00.

	Time variables					
Time point	ECG start	Defib shock	First compression	Last compression	VF onset	ROSC pulse
Abbreviated	ecgtm	shktm	fctm	lctm	vfonsettm	rsctm
Correct	33	138	90	108	45	15
Wrong	4	2	0	1	5	0
Missing	17	0	50	31	90	125

of first and last compression. Missing values were noted in 17 cases due to lack of a recorded value in the manual database. The automatic procedure used the date stamp found in the defibrillators files composing the CPR process data and therefore was always available.

For the time of shock (shktm), there are two errors propagated from deviations in ECG start time.

For the time of first compression (fctm) there are 50 deviations categorized as missing. In six of these cases the manual registration has provided a time for start of chest compressions corresponding to ECG start time. The algorithm has been designed to interpret this situation as "ongoing chest compressions" at the start of recording (see Appendix B.4 for details). One case is propagated from the large deviation in ECG start time (ectm). In the remaining 43 cases the algorithm produces the same missing codes as were used in the manual registration.

For the time of last compression (lctm) there is one error corresponding to a deviation of two seconds which we do not consider to be unacceptable. There are 31 cases coded as "missing." There is one "missing" case where fc is given a time and lc is coded as unknown in the manual registration. The algorithm was designed to handle several variations of special coding of lc/fc and this is the only case not handled (see Appendix B.5 for details). One case corresponds to the deviation propagated from ecg start time. In the remaining 29 cases the algorithm produces the same missing codes as were used in the manual registration.

For the time of VF onset (vfonsettm) there are five deviations considered as errors. Four of these errors are deviations in the range 21-22 seconds. In the manual registration vfonset is set at 11-12 seconds after start of shock. In these cases VF is also annotated as reappearing 30 seconds after shock (r30). The algorithm makes the determination of VF onset at r30 and produces this offset in time compared to the manually derived reading by the reviewer. This discrepancy between the manual review time and the automatically derived algorithmic time appears to be explained by inaccuracies in determining the time point for the end of the shock. When the manual review noted the time at 10 seconds to be asystole and also recorded the vfonset to be in the 11–15-second range, the algorithm would define VF onset at the next rhythm time check at r30. (See Appendix B.6 for details.) There is one case where the deviation is one hour and the manual registration obviously is wrong as the time given precedes the start of episode. There are also six cases considered as "missing" where the manual registration has provided a proper time which the algorithm has interpreted as persistent VF. In all these cases the manual rhythm annotations prior to and after shock (rhyb4, r10, r30, and r60) indicate VF. The algorithm is designed to recognize these cases as persistent VF (in 38 cases the algorithm and manual registration coincide). There are two cases considered as missing where the manual interpretation indicates persistent VF while the algorithm has yielded a proper time. In the first case the manual rhythm annotations at 10 and 30 seconds after shock indicate asystole and VF, respectively (r10 = 1 and r30 = 2). This is interpreted by the algorithm as VF reappearing at 30 seconds. In the second case shocks 2 and 3 are not registered. The study is designed on the assumption that the episode registrations are complete. In this case, the rhythm annotations will not be correct as two shock registrations are missing. There is one case where the manual interpretation has used the code for persistent VF while the algorithm has used the "missing" code 88 : 88 : 88. In this case the preshock rhythm is VF and the rhythm at ten seconds is "unknown." The algorithm has not been designed to recognize this as persistent VF (in 43 cases the algorithm and manual registration coincide). So in 81 out of the 90 cases categorized as missing, the algorithm produced the same missing codes as were used in the manual registration.

For time of ROSC (rsctm) there are 15 correct registrations and 125 considered as missing. The only differences are discrepancies in the use of codes for "unknown" 99 : 99 : 99 and 88 : 88 : 88 which the algorithm is not able to distinguish and therefore uses the "unknown" code consistently.

4.2. Evaluation of the Replication of the Patient Response Variables. The patient response variables are coded as correct if the manual and automatically generated values are identical. Otherwise the automatically generated variable is considered wrong. The patient response variables are shown in Figure 5 (for additional detail see Table 7). For the initial rhythm (init_rhy) there are no errors.

For the preshock rhythm (rhyb4), there are four errors. In three of these cases the last rhythm registration prior to the previous shock deviates from what has been manually determined as the preshock rhythm. The algorithm determines rhyb4 from the last registration prior to the current shock (r120, vfonsettm, or rosconsettm). The fourth error corresponds to the case of two missing shock registrations which corrupts the generation of RORE.

Table 7: Results for the comparison between manual and automatic recording of patient response variables. The table counts the number of correct and wrong values. An automatic recording is considered correct if the automatic recording is identical to the manual recording. Otherwise the recording is considered wrong.

	Response variables								
Variable name	Initial rhythm	Preshock rhythm	Rhythm 10 secs after the last shock	Rhythm 30 secs after the last shock	Rhythm 60 secs after the last shock	Rhythm 120 secs after the last shock	VF prior to next shock?	Organized rhythm prior to next shock	ROSC
Abbreviated	init_rhy	rhyb4	r10	r30	r60	r120	vfpr	orgpr	rosc
Correct	140	136	135	136	137	134	138	133	127
Wrong	0	4	5	4	3	6	2	7	3

There are five errors for the rhythm at 10 seconds after shock (r10). For four of these cases, the manual registration indicates a non-VF rhythm. At the same time, the manual registrations of the time for VF onset (vfonsettm) are 13–16 seconds after shock. This will be reflected in the generation of RORE and the algorithm will look for rhythm transitions in a time window of five seconds that are present ten seconds after end of shock (end of shock is set to three seconds after shock is delivered). Thus, the algorithm will find a rhythm transition to VF corresponding to the registered time of VF onset. The fifth error corresponds to the case of two missing shock registrations which corrupts the generation of RORE.

There are four errors for the registration of the rhythm at 30 seconds after shock (r30). All of these are cases where the algorithm indicates VF corresponding to a VF onset time set at 30–35 seconds after shock rather than the manually registered non-VF rhythm. The explanation for this is similar to the one given for r10 above.

For the rhythm at 60 seconds after shock (r60) there is one case corresponding to the problem with VF onset and one corresponding to the 2 missing shock registrations both described above. The third error corresponds to a case where the manual registration has provided an unknown rhythm. In RORE, the transition to unknown rhythm will occur at 60 seconds. In the case of transition to unknown rhythms around the time point under consideration the algorithm is designed to choose the last known rhythm as long as it is present within the time window. This special handling was designed to handle transitions to unknown rhythms generically but does not work well when the time of rhythm transitions are not accurately represented. For the rhythm at 120 seconds after shock (r120) there are six errors. There are two cases corresponding to the problem with VF onset and one corresponding to the 2 missing shock registrations both described above. In another case, the manual registration indicates a proper rhythm while the algorithm has determined the rhythm as "unknown." Here the ECG recording ends at 111 seconds after shock. This is represented in RORE as unknown rhythm (UN) and the algorithm consequently sets the rhythm at 120 seconds as "unknown." There is also one case where the time of ROSC onset is 100 seconds after shock and the manual registration at 120 seconds indicates a transition to "unknown rhythm." In this case, the algorithm will indicate the last known proper rhythm as described above. There is also a case with mismatch between "undetermined" and "unknown" rhythm.

For the indication of whether VF occurs prior to the next shock (vfpr), there are 2 errors. In both cases there is no evidence of VF in the interval in question. In one of the cases the algorithm states that there is no VF, contradicting the manual registration of "yes." In the other case, the algorithm indicates "unknown" in contrast to the manually registered "no" because the rhythm annotations indicate "unknown" or "indeterminate" rhythm.

For the indication of whether an organized rhythm occurs prior to the next shock (orgpr), there are 7 errors. One error corresponds to the last error described above where there is no evidence of organized rhythm in the interval in question. The algorithm indicates "unknown" in contrast to the manually registered "no" because the rhythm annotations indicate "unknown" or "indeterminate" rhythm. One of the other errors is due to the problem with the two missing shocks described above. In the five remaining cases, the rhythm annotations indicate an organized rhythm in the interval in question which the algorithm recognizes and determines "yes" in contrast to the manual registration of "no."

For the indication of presence of ROSC (rosc) there are 13 errors. In eight cases, the ROSC time is "no" and the manual indication of ROSC is "yes." The algorithm does not interpret this correctly as it bases its interpretation from RORE which does not carry information about any occurrence of ROSC. In the five remaining cases the ROSC time is "indeterminate" and the algorithm indicates "no" ROSC as there is no evidence of ROSC in RORE while the manual registration says "unknown."

4.3. Evaluation of the Replication of the Therapy and Device Operation Variables. The results for the therapy and device operation variables are shown in Figure 5 (for additional detail see Table 8). The variables are considered correct if the manually registered and corresponding automatically generated variables are identical.

There are no errors for the variables indicating shock number (shkn), number of shock sequences (ssrecord), and number of shocks in sequence (shks).

For the variable indicating the mode of the AED at the time of shock (mode) there are 21 errors which all correspond to the algorithm providing "yes" rather than "no" for manual

Table 8: Results for the comparison between manual and automatic recording of device operation and therapy variables for the data set. The table counts the number of correct and wrong values. For all variables except imp and enrgy an automatic recording is considered correct if the automatic recording is identical to the manual recording. Otherwise the recording is considered wrong. For imp and enrgy the numeric deviations between the manual and automatic recordings are considered. A deviation of zero is considered correct, and larger deviations are counted as errors.

	Therapy variables						
Variable name	Shock number	Number of shock sequences recorded	Number of shocks in sequence	Mode	EMS CPR prior to shock?	Impedance at 1st shock	Energy of 1st shock
Abbreviated	shkn	ssrecord	shks	mode	cpr	imp	enrgy
Correct	140	140	140	119	137	123	120
Wrong	0	0	0	21	3	17	20

mode. These are a result of the manual reviewer incorrectly assuming the mode was for automatic mode when in fact the device was in manual mode as indicated by the defibrillator process files.

For the variable indicating if there was EMS CPR prior to shock or not there are three errors. For two of the cases both start and end times of compressions prior to shock are set to "unknown." The algorithm consistently interprets this as CPR being present (reducing error rates in tuning phase). The third error is due to the problem with the four-hour mismatch in the ECG start time variable.

For the variable indicating the impedance at first shock (imp) there are 17 errors.

For the variable indicating the energy of the first shock there are 20 errors.

The algorithm registers the impedance and energy for each individual shock. For these variables (except cpr) the automatically derived information is read directly from the log data file and is therefore exact. It is therefore an error caused by the person performing the manual extraction estimating the value and is not due to errors in the reasoning process of the algorithm.

5. Discussion

We have presented a method for replicating the manually annotated variables in an EMS registry database. The method was developed according to the principles presented by Eftestøl et al. [8] and implemented in MATLAB. To our knowledge, this is the first time automated review has been performed on resuscitation data.

In addition, the times, impedances, and defibrillation energies were obtained directly from the device logs and were inherently more accurate than visual estimates by reviewers. One of the main objectives of this study was to verify how closely the automated review can approximate the original data when one has access to the true annotations. These annotations are also the key information components used in the construction of the response and therapy representations that is fundamental to this method. As we discussed in the methods section, we used these representations to identify the shocks and determine the pre- and postshock events for each of these.

For the time variables, deviations larger than 1 second were categorized as errors. 5 seconds seems more appropriate as 1 second is very restrictive and identifies differences that are too small to be clinically significant. We suggest using a 5-second threshold in future studies. In the test data, there were only two errors in the 2–5-second range.

In the evaluation of the results, we have used the terms correct and wrong, but it is important to consider that we are really considering deviations between the manual and automatic registrations. The detailed review of the deviations showed that some of these were caused by errors in the manual registrations and others by errors in the automatic registrations. For the time variables, determining the vfonset was one such example where the problem was identified to be associated with the fact that manual interpretation of persistent VF is done in a time interval after shock and that the endpoint of a shock is not clearly defined for manual interpretation which it has to be for automatic interpretation. Otherwise, it seems that the algorithm greatly improves the accuracy over the human reviewer and is much more accurate. The machine is accurate to the millisecond providing that it has been properly synchronized to a "GMT" time and that relative times are clearly accurate to a millisecond barring machine malfunction. Human reviewers can only be accurate to about 1 to 2 seconds as we have shown in this work. As for the patient response variables, errors in the evaluation 10 seconds after shock can largely be associated with the nonprecise definition of the end of shock time. There are also errors that are caused by inconsistencies in the manual annotations. Generally speaking, the manual interpretation might cause errors in the sense that two different variables express the same information, like, for example, last rhythm change in the postshock period which is the same as the preshock rhythm in the next preshock sequence. The automatic annotations base its interpretation on considering the rhythms between uniquely defined rhythm transition times and thus avoids these kinds of inconsistencies. As for the interpretation of ROSC the algorithm does not interpret this correctly as it bases its interpretation from RORE which does not carry information about any occurrence of ROSC. For this case, the rhythm interpretation should distinguish between pulseless and pulse giving organised rhythms. For the therapy and device operation variables, the errors will mostly reflect errors in the manual registration as the algorithm reads this

information directly from the electronic log files which will be reliable as long as the correct information is read. We have shown that we can replicate the review process of a given EMS system fairly accurately. To further develop this system and to handle the errors in the algorithms one would need to adjust the manual review process so that the critical time points are more clearly defined, make a dedicated study, and compare automatic and manual registrations again to see if errors are reduced. In an implementation, the automatic registrations should be checked and overread by a clinician.

The comparison shown above (Figure 5) demonstrates the inherent variability of a human reviewer in interpreting the data from the arrest and indicates several areas in which improvement can be made using an automated reasoning algorithm. One clear necessity is that all of the definitions must be made explicit so that a rule can be applied that will in every case provide the same result. This would allow the coding of computer algorithms to follow these definitions. In several cases (i.e., if VF that recurs after a shock is "persistent" or "recurrent" may depend on the duration of the period of asystole occurring after the shock). This study also clearly demonstrates that computer logs and times should be used in all cases as being more reliable than estimates and error prone manual data entry by reviewers. In this study the mode of defibrillator operation was incorrectly inferred by the reviewers in a high proportion of cases when the defibrillator log was able to provide this information accurately from the digitized files. In addition, a large number of errors which are "propagated" because the initial time point is unknown or recorded incorrectly can be reduced by improvements in using the time stamps from the defibrillator logs directly. These are examples of systematic deviations that further work with automatic methods of analysis can readily be programmed to reduce and eliminate.

The next step in developing this system will be to develop algorithms for automated rhythm annotations and chest compression detections. Our approach to do that will be to extract rhythm segments from the ECG tracings and categorize them according to the annotations used in the registry. The start and end points for each of these segments can be determined by using the same representations constructed in the present study. For example, all ECG tracings of VF segments without CPR artifacts can be found by searching the combined representation for each patient episode for the string "VF." For all matches the VF segments can then be extracted from the ECG tracing as specified by the interval start and end sample given in the representation. Furthermore, signal processing algorithms for discriminating between the different rhythm categories will be developed. The discriminative power of these algorithms can be evaluated against the categorized collection of labeled rhythm segments. Correspondingly, methods for detecting chest compressions will be developed, applying the same principles for collecting segments with ongoing compressions from the signals carrying information about the presence of chest compressions. In this way, an EMS specific annotator can be made. This rhythm detector will replicate annotations as verified by blinded review by experts. Once rhythm and chest compression annotations are automated, the same algorithms used in this study for the construction of the representations from the manually extracted data can be applied. To evaluate the system, the performance of the fully automated system can be compared to the performance of the semiautomated and "expert reviewed" system which can be regarded as the gold standard.

In the current study, the presence of chest compressions was evaluated based on the compression depth signal derived from the acceleration measurements from the chest compression puck placed on the victim's chest. In the case where such information is not available, one might consider using the impedance data to follow respirations and one of our group is looking at how reliable this might be and also into adding the ETCO2 to the detail when it is available. The use of impedance for determining presence of CPR has been found to be reliable in a study by Stecher et al. [14]. This will allow the automatic reading using impedance in machines from other manufacturers who do not have the "puck" and in instances where the puck is not used even though it is at the scene. The impedance can also be used to automatically determine the presence of ventilations [15] and circulation [16] which has been demonstrated by Risdal et al. A future RORE can be extended to include information about ventilations, circulation, and possibly drug administration.

One method to validate the automatic analysis of the rhythm states would be for three expert reviewers to independently review the rhythm transitions and classifications as performed by the algorithm and to indicate errors or disagreements. One might then classify an "error" as any indication of disagreement with the algorithm that is noted by at least 2 of the 3 reviewers. Consideration of when the automatic method is accurate enough to be used without expert "overreading" would be based on a low error rate, perhaps less than 1%.

Of course, there are variables in the registry database that require manual interpretation. For example, there are variables describing the cause of CPR interruptions related to each shock and other variables for describing use of medications. The registration of these variables will still require manual interpretation.

Once a fully automated system is considered to perform satisfactorily, it will not only increase the efficiency for data interpretation at the EMS system from which it has been developed. It will also be possible to apply the automated review system to data from other EMS systems, thus enabling efficient multicenter data analysis without the need for centralized data storage. The results generated from data in this fashion will in general be anonymous with respect to issues of patient confidentiality. This method does access the CPR process data directly in the format downloaded from the AED device, thus making it independent from the local database structure used by the EMS. Thus interfacing the system directly to the raw data should make it easier to adopt it at other EMS sites with different registry database structures. Software interfaces will have to be adapted to read clinical information and translate it into the appropriate format.

In the present study we only considered a population of patients restricted to those treated with Philips AED device. In the case that we want to study data from different EMS services, the algorithms should also be able to handle data from other types of AED devices. One of the important aspects of this work is that as long as we are able to construct the state sequence models, we can apply the algorithms. So as long as the primary information objects are available through interpretation of the CPR process data it will be possible to apply the methods described here, independent of the type of AED device. Another objective of the present study was to demonstrate the applicability of the resuscitation data representation scheme presented by Eftestøl et al. [8]. The scheme was developed without knowledge of the data review method used in the King County EMS system. As was stated in that study, "We have discussed a methodology for representing resuscitation data emphasizing that such a representation scheme should offer a flexible format for efficient analysis of a variety of resuscitation research objectives." In the present study we have demonstrated that the representation scheme offers a flexible format for efficient analysis. By applying the method to a research objective for which it was not originally intended, the representations in the three domains have been shown to be robust as well.

6. Conclusion

We have demonstrated that it is possible to use the information present in the CPR process data recorded by the AED during resuscitation along with rhythm and chest compression annotations to automate the episode review. This automated review is based on representing the resuscitation episode with sufficient detail using a minimal but sufficient set of transitions between rhythm states and therapy states which can be combined into a representation of the resuscitation episode which communicates the necessary information in a brief and compact format. This method can be automated to allow the development of a large database of resuscitation data for use in clinical studies of care and therapy for the cardiac arrest patient.

Appendices

A. Supplement—Reasoning from the Representation Back to Create the Derived Data

A.1. Time Data Conversions. The initial time event retrieved from the defibrillator is the "powerCycleOn" which corresponds to the time the ECG recording is started (0 seconds). This date stamp gives the date and time ("yyyy:mm:dd:hr:mn:sc") at the start of the recording and is used to determine "ecgtm." The datestamp is converted to a serial date number ("SDN_time") which gives the time in number of days from January 1, 0000, and this is the SDN_time for the start of the recording. This initial event is called "Start_SDN." The time as recorded in the RORE for all subsequent events found in the representations can then be converted to the SDN_time by taking the time (in seconds) recorded in the RORE for that event and convert it to an SDN_time which is in "Days Since 0000" as follows: SDN_time = Start_SDN + (Event_Seconds/60/60/24). The second term converts the number of seconds elapsed to the number of days elapsed as coded in SDN_time. Thus, to reason backwards, in order to determine the shock times in SDN_time from the RORE times recorded in seconds, the representation is searched for the symbol used to identify a shock, "D." The time interval in seconds that coincides with each match is then converted to the SDN format which provides the elapsed time in days from Start_SDN. When this elapsed time is added to the Start_SDN it gives the year, date, and time accurately as encoded in the SDN format. This format could be used by itself as a reliable and reproducible time variable. In this study the data in the original ACCESS database was in the hour:minute:second format. For this reason we transformed the SDN format to hr:mn:sc format so that the derived data could be compared with the original data directly.

A.2. Determining the Postshock Rhythms at 10, 30, 60, and 120 Seconds. The postshock rhythms along with the start, end time and duration of each rhythm are derived from the postshock interval as it is displayed in the episode representation. If the rhythm at 10 seconds after shock is to be determined, the postshock rhythm with the transition time closest to ten seconds bounded upwards to 15 seconds is allocated to the variable "r10." The same procedure is repeated for the variables "r30," "r60," and "r120" (always looking 5 seconds beyond the time in question).

B. Supplement to the Results Section

B.1. Systematic Deviations in the ECG Start Time. When it comes to deviations in ecgtm, the algorithm differs between systematic and nonsystematic deviation. In the result evaluation of the manual and the automatically generated variables these two types of deviations were handled differently. When the manual given time was 00:00:00 or 12:00:00, these are considered systematic and are compensated for in the evaluation of error so that a single early or initial deviation does not propagate to the subsequent time variables. These deviations are not considered as errors. For ecgtm the code "missing" is used. The nonsystematic deviations are not compensated for in the evaluation of the other variables and possible systematic components in the deviations might propagate and be counted as errors in the other time variables.

B.2. Use of Special Codes for "Missing" Information. In the original database several codes were used to indicate persistent VF recurring immediately after a defibrillation shock, "no CPR data available" due to failure to use the puck or other technical problem and "unknown" when no information could be recorded because of severe artifact, failure to record, and so forth.

B.3. Nonsystematic Deviations in the ECG Start Time. A possible explanation for these errors might be that defibrillator was turned on and the leads were not attached to the patient for about 1 minute in two of these cases and that the manual abstractor started the "ECG time" when the leads were hooked up, but the "auto" reading from the CPR process defibrillator data gives the time when the device was turned on. This is an error of process in the manual part because the reader interprets the start differently from the machine start.

B.4. Deviations Categorized as Missing for the Start of Compression Times. These are all cases where fctm is manually registered to be at the start of the ECG recording or previous to this. The algorithm sets the state of therapy to "unknown" in the period prior to the start of the ECG recording. The corresponding therapy representation will then start with the symbols U, C where the time for the transition to compressions corresponds to the ECG start time. When the algorithm interprets this symbol sequence, it determines fctm as unknown. This was a way of handling the cases were the manual registration of "fctm" was "unknown" (41 cases).

B.5. Deviations Categorized as Missing for the End of Compression Times. In RORE this is coded with the end of the compression sequence coinciding with the defibrillation. In some cases where both fctm and/or lctm are coded as "unknown," the RORE will set fctm to correspond to the start of ECG recording and lctm to correspond to the time of defibrillation. This is unrealistic but was done so that the algorithm could be designed to recognize the case of both variables manually registered as "unknown." This is the sole case where only lctm is registered as "unknown" so the algorithm was not designed to recognize this.

B.6. Deviations in VF Onset Time. The algorithm evaluates rhythms with reference to end of the shock which is set to 3 seconds after start of shock. In all these cases, the variable indicating the rhythm prior to shock (rhyb4) has been annotated as VF while the annotation for the rhythm at ten seconds after the shock given as non-VF. In RORE, the transition time to non-VF is set at ten seconds, and the algorithm interprets this as a VF that persists for less than 10 seconds after shock which is not considered when looking for vfonsettm. If it lasts longer it is considered persistent. This is a problem that arises because there is no accurate rhythm annotation immediately after shock. This error could be eliminated by using the shock time as a rhythm transition point. Essentially the rhythm would be considered "unknown' until the ECG voltage returned to baseline after the shock at which time a determination could be made.

C. Detailed Explanation of the RORE in Figure 4

The time shown corresponds to 0 to 1057 seconds. The tracings shown in Figure 3 correspond only to the period from 180 to 330 seconds. The left column is the therapy representation, showing the therapeutic interventions. For the first 46 seconds there is no ECG, so this is represented by "UN" (unknown therapy). At 46 seconds recording of ECG starts and compressions are observed on the compression depth signal. At 180 seconds, the chest compressions are interrupted and a hands off interval follows (represented by an "H") and lasts until a shock is given at 196 seconds (represented by a "D"). The remainder of the case shows similar sequences of hands off interval, chest compressions, and defibrillations until no further annotations are given at the end of the recording.

The patient response representation is shown in the middle. It represents the same time span, showing the cardiac rhythms presented by the ECG. As for the therapy representation, the rhythm for the first 46 seconds is unknown ("UN"). At 46 seconds, the initial rhythm was recorded as "VF." The next observation was made at 208 seconds (ten seconds after shock) and asystole was recorded ("AS"). This continued until 258 seconds where an organized rhythm was observed ('represented by "PE"). The remainder of the case shows similar transitions between rhythms, first to "VF" and then to "PE" again and finally ROSC at 469 seconds. The documentation of rhythms ends at 856 seconds.

The episode representation combines the therapy and response representations showing the interaction between therapy and response. From 46 to 190 seconds, compressions are provided during VF. Compressions are interrupted at 180 seconds, preparing for the shock given at 196 seconds. The effect of the shock is observed at 208 seconds. This is an effect of the extrapolation of the response representation from the spreadsheet information. The true transition time should be prior to this. Following this, the effect of the compressions is evident through transitions from asystole to organized rhythm and then to VF. Following this compressions are interrupted and a new shock is given resulting in an organized rhythm and finally ROSC before documentation ends.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Review Article

Rhythm Analysis during Cardiopulmonary Resuscitation: Past, Present, and Future

Sofia Ruiz de Gauna,[1] Unai Irusta,[1] Jesus Ruiz,[1] Unai Ayala,[1] Elisabete Aramendi,[1] and Trygve Eftestøl[2]

[1] *Communications Engineering Department, University of the Basque Country (UPV/EHU), Alameda Urquijo S/N, 48013 Bilbao, Spain*
[2] *Department of Electrical Engineering and Computer Science, Faculty of Science and Technology, University of Stavanger, 4036 Stavanger, Norway*

Correspondence should be addressed to Sofia Ruiz de Gauna; sofia.ruizdegauna@ehu.es

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Survival from out-of-hospital cardiac arrest depends largely on two factors: early cardiopulmonary resuscitation (CPR) and early defibrillation. CPR must be interrupted for a reliable automated rhythm analysis because chest compressions induce artifacts in the ECG. Unfortunately, interrupting CPR adversely affects survival. In the last twenty years, research has been focused on designing methods for analysis of ECG during chest compressions. Most approaches are based either on adaptive filters to remove the CPR artifact or on robust algorithms which directly diagnose the corrupted ECG. In general, all the methods report low specificity values when tested on short ECG segments, but how to evaluate the real impact on CPR delivery of continuous rhythm analysis during CPR is still unknown. Recently, researchers have proposed a new methodology to measure this impact. Moreover, new strategies for fast rhythm analysis during ventilation pauses or high-specificity algorithms have been reported. Our objective is to present a thorough review of the field as the starting point for these late developments and to underline the open questions and future lines of research to be explored in the following years.

1. Introduction

In the early 1990s, the American Heart Association (AHA) established the chain of survival [1] to describe the sequence of actions for a successful resuscitation in the event of an out-of-hospital cardiac arrest (OHCA). The chain of survival involves four links: early recognition, early bystander cardiopulmonary resuscitation (CPR), early defibrillation, and early advanced care. The most influential factor explaining survival is the interaction between CPR and defibrillation administered in the first minutes from collapse [2]. Survival from witnessed ventricular fibrillation (VF) decreases by 10–12% for every minute defibrillation is delayed [3, 4], but when CPR is provided the decline in survival is only 3-4% per minute [4–6]. CPR and defibrillation can be successfully taught to laypeople, and the use of automated external defibrillators (AED) by the public may shorten the time to defibrillation [7].

Over the years, evidence has accumulated suggesting that minimizing the interruptions in chest compressions during CPR is determinant for survival from OHCA [8–11]. Consequently, current resuscitation guidelines emphasize the importance of high-quality CPR with minimal interruptions in chest compressions [12, 13]. However, CPR must be interrupted for a reliable AED rhythm analysis. The mechanical activity from the chest compressions introduces artifacts in the ECG that substantially lower the capacity of an AED's shock advice algorithm (SAA) to detect shockable (sensitivity) and nonshockable (specificity) rhythms [14, 15]. Interruptions for rhythm analysis alone take between 5.2 s and 28.4 s in commercial AEDs [16]. These interruptions, known as hands-off intervals, adversely affect the probability of restoration of spontaneous circulation (ROSC) after the delivery of the shock [17] and compromise circulation [18]. In fact, a recent multicenter study found an 18% decrease in survival to hospital discharge for every 5 s increase in

preshock pause length [19]. Therefore, reliable rhythm analysis methods during chest compressions would be of great value.

Over the last 15 years, many efforts have been made to reliably analyze the rhythm during CPR. Strategies have focused either on adaptive filters to suppress the CPR artifact [20] or, more recently, on approaches based on the direct analysis of the corrupted ECG. Most studies report sensitivities above 90%, the minimum value recommended by the AHA for AED performance [21]. However, the specificity rarely exceeds 85%, well below the 95% AHA goal. As Li and Tang phrased it back in 2009, performance is *good but not enough* [22]. In addition, the impact these methods would have on CPR delivery is unknown. The current evaluation standard is based on the sensitivity and specificity of a single analysis using short duration (10–20 s) segments. This does not reflect the real application scenario in which the objective would be to continuously analyze the rhythm during CPR. In this context, the fundamental question is whether rhythm analysis improves CPR delivery compared to the standard treatment, that is, cycles of 2 minutes of uninterrupted CPR followed by a hands-off interval for rhythm assessment. This change of focus was stressed by the International Consensus on CPR and Emergency Cardiovascular Care Science with Treatment Recommendations (CoSTR) in 2010 [23].

Recent developments preclude the start of a new era in the field of rhythm analysis during CPR. A new methodology has just been developed to measure the impact of continuous rhythm analysis on CPR delivery [24]. In addition, new ideas have been explored, like the possibility of assessing the rhythm during ventilation pauses [25] using SAAs capable of diagnosing the rhythm in less than 5 s [26]. At this point a review paper that goes beyond the compilation and summary of filtering methods is well justified. Our objective is to present a thorough review of the field as the starting point for these late developments and to underline the open questions and future lines of research to be explored in the coming years.

The paper is structured as follows. Section 2 describes the characteristics of the CPR artifact and presents the problem of rhythm analysis during CPR. Section 3 is a review of the approaches to rhythm analysis during CPR up to year 2012, grouped by the evaluation methodology. Section 4 describes a new methodology to quantify the impact on CPR delivery of rhythm analysis during chest compressions. Section 5 presents the late developments in rhythm analysis during CPR.

2. Context

Chest compressions introduce an artifact in the ECG that substantially modifies its waveform. For example, Figure 1 shows three OHCA segments where CPR corrupts the ECG during the first 15 s of the segment. During the last 15 s chest compressions ceased, revealing the underlying rhythms: VF, pulseless electrical activity (PEA), and asystole. During CPR, the artifact sometimes resembles a regular rhythm with rates around 100 compression per minute (cpm). In these case the AED may give a wrong no shock diagnosis if the underlying rhythm is shockable, that is, VF or fast ventricular tachycardia (VT). Conversely, chest compression artifacts may also introduce fast and disorganized artifacts which might cause an erroneous shock diagnosis if the underlying rhythm is nonshockable. Consequently, the accuracy of commercial AEDs substantially decreases in the presence of CPR artifacts. For example, sensitivity/specificity values of 58.4%/90.8% and 81.5%/67.2% have been reported [14, 15], although these figures are extremely dependent on the design characteristics of each SAA.

The origin of the CPR artifact is not fully understood. Langhelle et al. [32] conjectured that the CPR artifact is an additive noise and identified four possible sources for the artifact: the mechanical stimulation of the heart, the mechanical stimulation of the thoracic muscles, electrode tapping or dragging, and static electricity. Later, Fitzgibbon et al. [33] experimentally concluded that the main source of noise was the skin-electrode interface, specifically, that the noise was related to the electrical properties of the electrode. When chest compressions are delivered manually the characteristics of the artifact are very variable and depend on how the compressions are administered (rate, depth, and pauses) and on the characteristics of both the patient and the recording system.

The nature of the CPR artifact is best analyzed when CPR is performed on patients in asystole (no underlying heart rhythm) because the ECG only reflects the presence of the artifact, as shown in the last example of Figure 1. The artifact presents an almost periodic waveform, with its fundamental frequency being that of the chest compressions. However, the waveform and spectral characteristics of the artifact are very variable within a resuscitation episode and between episodes. Within an episode these variations may reflect changes on how CPR is administered by a rescuer, rescuer fatigue, or the intervention of several rescuers. For example, Figure 2 shows two short segments of CPR artifacts with very different waveforms and spectral content. In addition to its interpatient and interrescuer variability, on average the artifact presents an important spectral overlap with human ECG recorded during cardiac arrest. This is best seen by analyzing the power spectral density (PSD) of the CPR artifact and the different OHCA rhythms, as shown in Figure 3 for shockable (VF and VT) and nonshockable (PEA and pulse-giving rhythm, PR) rhythms. As shown in the figure the overlap is specially large for nonshockable rhythms, which anticipates the challenge of rhythm analysis during CPR for underlying nonshockable rhythms.

In conclusion, a reliable rhythm analysis during CPR involves advanced signal processing techniques to address the time-frequency variability of the artifact and its spectral overlap with human OHCA rhythms. These techniques are described in the following section. To conclude, Figure 4 illustrates the use of an adaptive filter for rhythm analysis during CPR. In the top panel of the figure the underlying VF is corrupted by CPR artifacts, although it is visible in the 5 s interval without chest compressions. The artifacts provoke erroneous no-shock diagnoses by an AED. Applying an adaptive filter reveals the underlying VF, and the AED correctly diagnoses the rhythm as shockable.

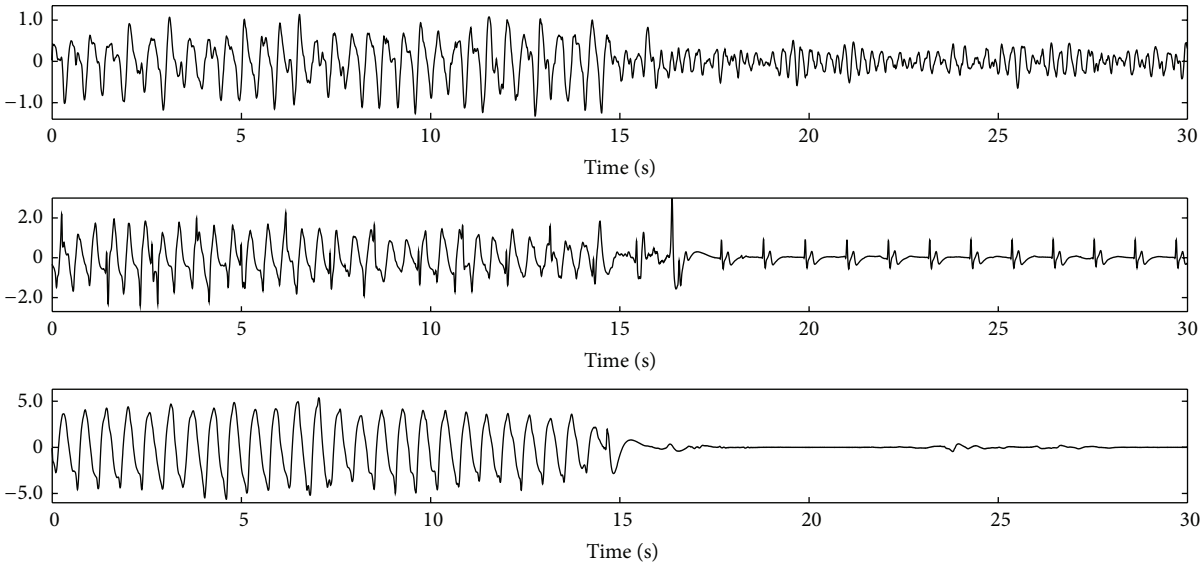


Figure 1: ECG segments in mV recorded in patients in OHCA. The top panel shows a VF, the middle panel shows a PEA, and the bottom panel shows an asystole. In all cases CPR artifacts corrupt the ECG in the initial 15 s interval. In the second 15 s interval chest compressions were stopped and the ECG shows the underlying rhythm.

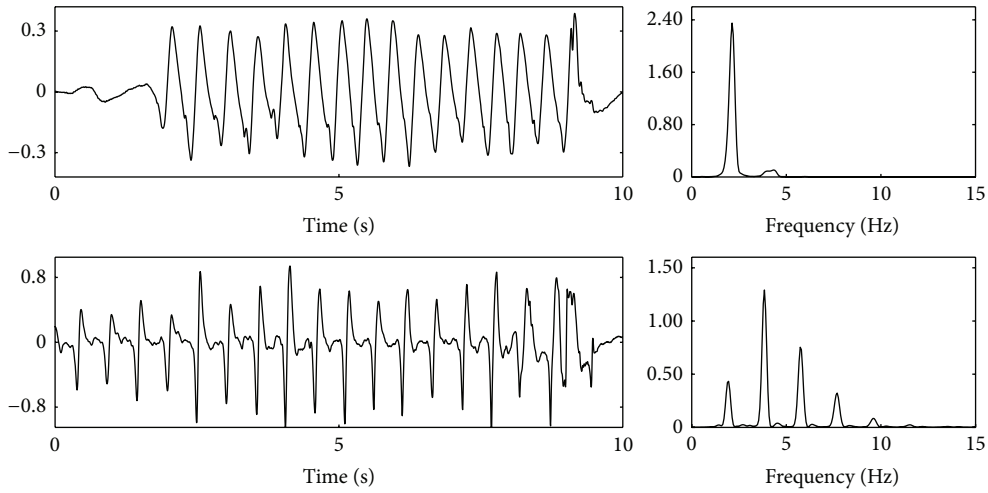


Figure 2: Two examples in the time and frequency domain of CPR artifacts recorded in OHCA patients in asystole. The figures show the ECG in mV and the normalized power spectral density (PSD) in the frequency domain. The first example has pauses in chest compressions, a rate of 133 cpm (2.22 Hz), and small harmonic content. The second example has no pauses, a rate of 116 cpm (1.93 Hz), and large harmonic content.

3. Overview of Rhythm Analysis during CPR

Research on the suppression of the CPR artifact started in the mid 1990s within the field of VF waveform analysis. VF waveform analysis for shock outcome prediction is beyond the scope of this paper; excellent reviews of this topic are available in the literature [34, 35]. In the first study by Strohmenger et al. [36] and in subsequent ones [37, 38], VF was induced in pigs and chest compressions were administered using a pneumatic piston at a constant chest compression rate of 80 cpm (1.33 Hz). The CPR artifact was successfully removed using digital high-pass filters with cut-off frequencies between 4 and 4.5 Hz [37, 38], because the dominant frequency of VF is around 9–11 Hz in pigs. However, in the human case VF dominant frequencies fall between 3 and 5 Hz [39], the spectral overlap with the CPR artifact is large, and the artifact cannot be removed using a simple high-pass filter [32, 39].

Given the characteristics of the CPR artifact, suppressing it from the human ECG requires adaptive filters, most of which use reference signals correlated with the artifact. Reference signals such as the thoracic impedance, the compression depth, or the compression force have been frequently used. Over the years many adaptive solutions have been proposed and evaluated. The methodology followed in these studies depended largely on the data available to the researchers.

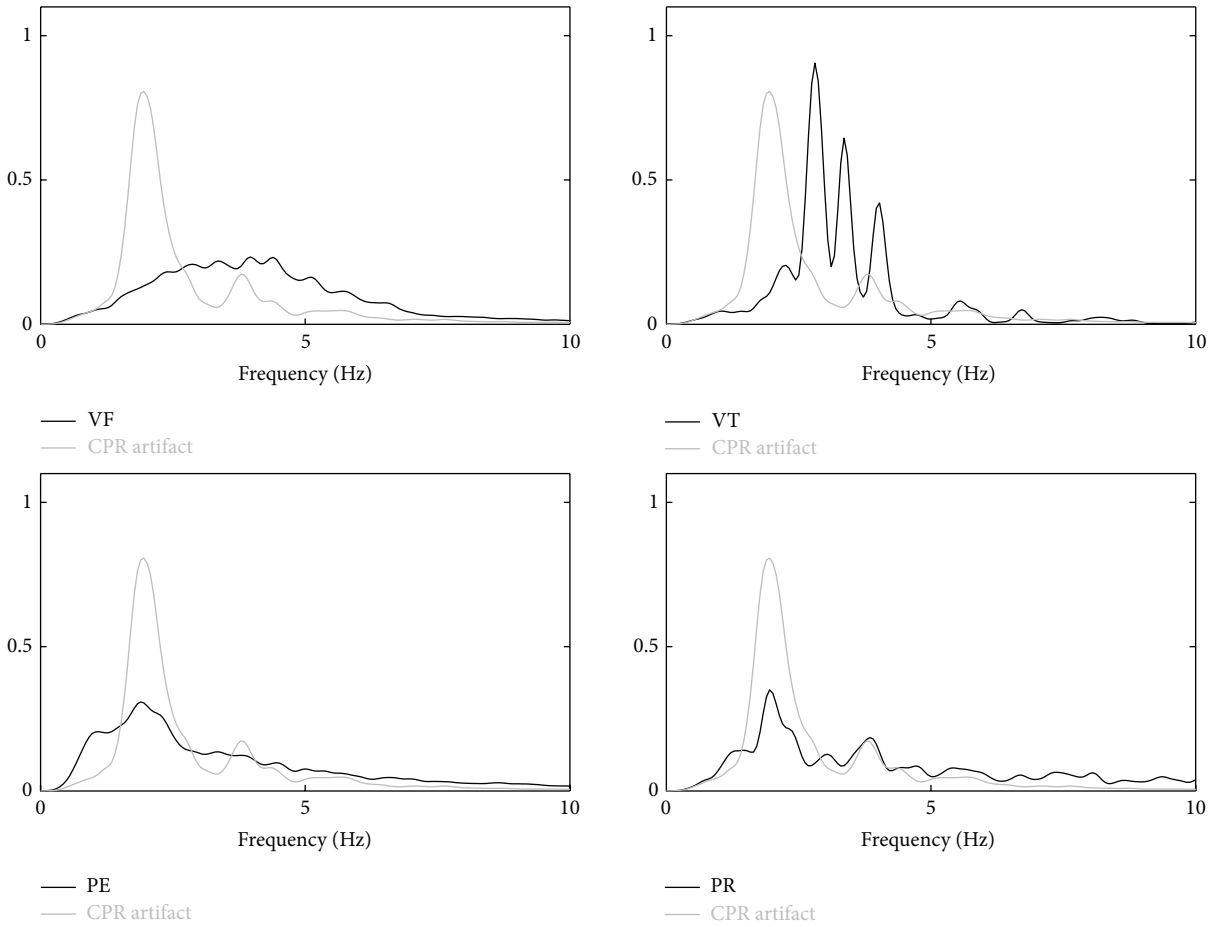


Figure 3: Normalized PSD of CPR artifacts (patients in asystole) and rhythms recorded during OHCA. The spectral overlap is large for both shockable (VF and VT) and nonshockable rhythms (PEA and PR).

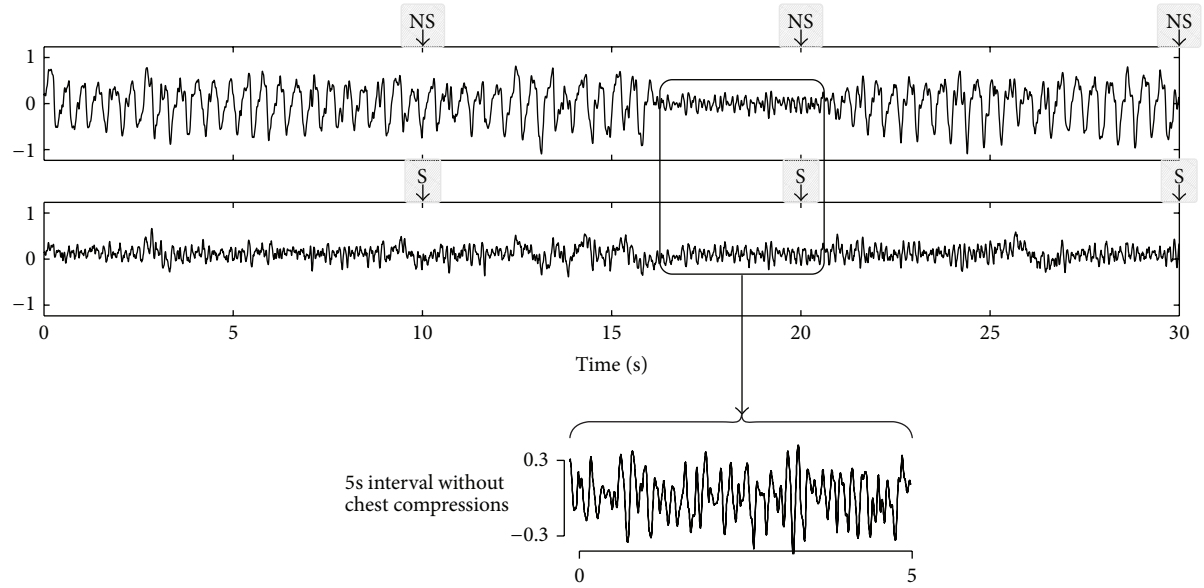


Figure 4: Filtering example for a VF recorded during OHCA. In the top panel the ECG is corrupted by CPR artifacts; a SAA from a commercial AED analyzes the rhythm every 10 s and gives erroneous no-shock (NS) diagnoses. In the bottom panel the CPR artifact is suppressed using an adaptive filter, the underlying VF is revealed, and the SAA gives correct shock (S) diagnoses. The underlying VF is visible in the 5 s interval without chest compressions.

Studies can be grouped into two broad categories: those based on the artificial mixture of ECG data and CPR artifacts and those based on cardiac arrest data recorded during CPR.

3.1. Studies Based on Artificial Mixtures. The mixture model was introduced early in 2000 by Langhelle et al. [32] and Aase et al. [40]. This model assumes that the CPR artifact, s_{cpr}, is an additive noise independent of the underlying ECG, s_{ecg}. Based on this assumption, filtering methods can be tested using independently recorded human ECG and CPR artifacts, added at different signal-to-noise ratios (SNRs) according to

$$s_{cor} = s_{ecg} + \alpha_{SNR} \cdot s_{cpr}, \quad \text{with} \quad \alpha_{SNR} = \sqrt{\frac{P_{ecg}}{P_{cpr} \cdot 10^{SNR/10}}}. \tag{1}$$

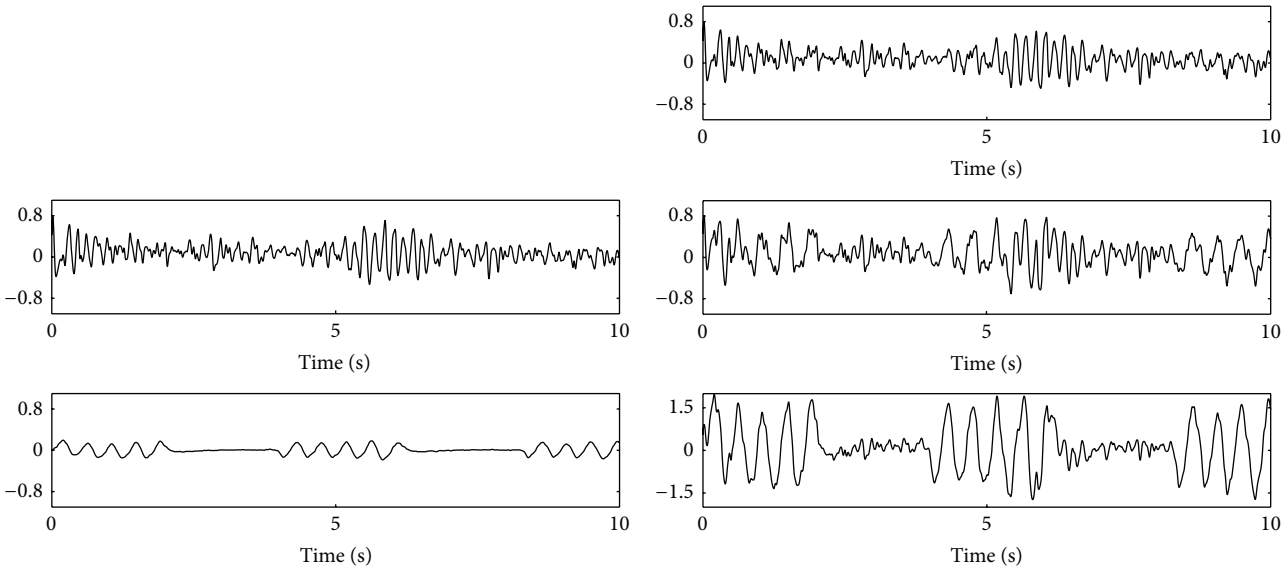
The SNR in dB is adjusted in the artificial mixture, s_{cor}, using the α_{SNR} coefficient, where P_{ecg} and P_{cpr} are the power of the underlying ECG and the CPR artifact, respectively. Figure 5 shows an example of how a human VF and a CPR artifact are combined when the additive model is used.

Typically these mixtures are formed with SNR values in the −10 dB (strong corruption) to 10 dB (low corruption) range. CPR artifacts are recorded during asystole, together with the reference signals used by the adaptive filters to model the artifact. The corrupted signal is fed to the filter which estimates the underlying ECG, and the estimated and the original ECGs are compared to quantify the efficiency of the filter in terms of the improvement of the SNR after filtering [32, 40]. In addition, the clinical accuracy of the method can be assessed using the filtered ECG to evaluate the sensitivity and specificity of an AED's SAA.

Langhelle et al. combined 25 human VF with CPR artifacts recorded from one pig, with CPR delivered by a mechanical device at a constant rate of 90 cpm (1.5 Hz). Their conjugate gradient adaptive filter could only use one reference channel besides the ECG (dual-channel methods), and the best filtering results were obtained for a reference that combined the thoracic impedance and the chest displacement measured at the mechanical device. Furthermore, when compared to a high-pass filter with 4.9 Hz cut-off frequency, their adaptive solution presented higher SNR improvement, with differences of up to 10 dB for low corruption levels. Aase et al. combined 200 human VF and 71 VT with CPR artifacts obtained from two pigs, with CPR delivered by a mechanical device at rates of 60, 90, and 120 cpm (1, 1.5, and 2 Hz). Although their Wiener filter could use an arbitrary number of reference signals (multichannel methods), they used only two: the thoracic impedance acquired via the defibrillation pads and the chest displacement. Not only they did optimize and test their method in terms of how filtering improved the SNR, but also they were the first to report the sensitivity of a SAA after filtering. They showed that the SNR after filtering was lower for higher compression rates (120 cpm) due to the increased spectral overlap and that filtering improved the sensitivity for low SNR. These results were extended by Husøy et al. [41] using the same human data combined with CPR artifacts recorded from pigs. This time CPR was delivered manually at 120 cpm rate, which reflects better the variability of the artifact found in real cardiac arrest episodes. The compression depth was calculated in this study from an external accelerometer based device [42]. Their Multichannel Recursive Adaptive Matching Pursuit (MC-RAMP) filter substantially lowered the computational demands of the Wiener filter and yielded comparable SNR results after filtering.

In a set of complementary studies, a group of Austrian researchers analyzed various dual-channel methods. They used an invasive arterial blood pressure signal as the reference to model the CPR artifact. They proposed two dual-channel methods, a Kalman state-space filter [43], and a filter based on the Gabor transform (time-frequency analysis) of the corrupted ECG and the reference signal [44]. These filters were optimized using mixtures of CPR artifacts recorded in pigs with 14 human VF samples. CPR was manually delivered at a rate of 80 cpm. Furthermore, Werther et al. [45] presented a comprehensive comparative assessment of these filters extending their rhythm database to 104 shockable and 281 nonshockable rhythms (other than asystole). Werther et al. compared the performance of four filters in a dual-channel configuration based on the blood pressure signal: their Kalman and Gabor filters, the MC-RAMP filter [41], and a recursive least squares (RLS) filter [46]. They tuned the filters for maximum SNR improvement and analyzed the performance of a SAA in terms of both sensitivity and specificity. All filters showed a comparable performance with good sensitivities, above 95%, but with specificities below 90%, caused by the higher spectral overlap of nonshockable rhythms with the CPR artifact. Later, Granegger et al. [47] applied independent component analysis (ICA) to 8 leads recorded in the surface of a dead pig after injecting human emergency ECGs close to the heart of the pig. Their database, which is fully described in [48], comprised 431 shockable and 487 nonshockable (20 asystole) records, with CPR delivered manually according to the 2005 guidelines. After applying ICA, they obtained a sensitivity of 99.7% and a specificity of 83.2% using the SAA of a commercial AED. These results marginally improved those obtained on the same data for the MC-RAMP filter using the force as reference [47]. Furthermore, a multilead configuration is not available in an AED environment.

Efforts have been made to adaptively filter the CPR artifact based only on the ECG because reference signals other than the thoracic impedance may not be available in AEDs. In these methods the fundamental frequency and harmonic content of the artifact are obtained from the spectral analysis of the corrupted ECG. These characteristics are then used to fit the adaptive filter, with solutions like an adaptive notch filter [49], a Kalman filter [27], or the coherent line removal algorithm [50]. Aramendi et al. [49] and Ruiz de Gauna et al. [27] introduced two methodological innovations by considering mixtures of shockable rhythms with CPR artifacts recorded from OHCA patients in asystole and by optimizing filter performance in terms of the sensitivity after filtering. In addition, Ruiz de Gauna et al. [45] used the mixture model to optimize their algorithm and reported their



(a) Two ECG segments independently recorded in humans during OHCA. The top panel shows the rhythm, a VF, and the bottom panel shows the CPR artifact recorded during asystole

(b) Linear mixtures of the original signals for three different corruption levels: low corruption (SNR = 6 dB) in the top panel, equal rhythm and artifact power (SNR = 0 dB) in the mid panel, and strong corruption (SNR = −6 dB) in the bottom panel

Figure 5: The mixture model: combination of a human VF and a human CPR artifact recorded from a patient in asystole at different SNR.

final results for human cardiac arrest data recorded during CPR.

However, adaptive filters based only on the ECG have poorer performance than adaptive filters using reference signals [27].

In summary, the mixture model is an excellent signal processing framework to test filter performance in terms of improvements in SNR and can serve well to optimize the parameters of a filter. However, SNR in real cardiac arrest data is not known, and how improvements in SNR are translated to the more clinically relevant sensitivity/specificity figures is not well understood [51] and may depend greatly on the SAA used. Finally, CPR may modify the dynamics of the underlying rhythm which violates the fundamental assumption of the independence of the ECG and the CPR artifact.

3.2. Studies Based on Cardiac Arrest Data Recorded during CPR. The limitations of the mixture model can be overcome using cardiac arrest data recorded while delivering CPR. During chest compressions the underlying rhythm is not directly observable, so these data are annotated by expert clinicians by assessing the rhythm in the intervals right after CPR and assuming the same rhythm for the preceding interval. Figure 1 shows three examples of these type of data: a VF, a PEA, and an asystole. Researchers then use short rhythm intervals (10–15 s) during CPR to optimize and test their rhythm analysis methods in terms of sensitivity and specificity. In this framework, rhythm analysis during CPR has been approached in two ways: adaptive filters followed by a SAA designed to diagnose artifact-free ECGs and new SAAs that directly analyze the corrupted ECG.

Most works covered in this section are based on human data, although a study by Berger et al. [46] investigated filtering schemes using an animal model of cardiac arrest. They induced asystole and VF in 13 pigs under normal sinus rhythm and delivered CPR to the pigs through a mechanical device (Zoll AutoPulse), which worked at a constant rate of 80 cpm [52]. They used an adaptive RLS filter based on the force signal provided by the compression device and analyzed the performance of three commercial AEDs. In these favorable conditions, porcine VF and low compression rates, they obtained a mean sensitivity and specificity of 97% and 95%, respectively, for 13 normal sinus rhythms, 8 asystole, and 109 VF records.

In 2004, Eilevstjønn et al. [14] published the first study that analyzed an adaptive filter to suppress the CPR artifact on recordings from OHCA victims. The study was based on data recorded in a clinical study [9] using a commercial defibrillator modified to acquire several additional reference signals, including those from a device to monitor CPR quality based on accelerometers. Eilevstjønn et al. adapted the MC-RAMP filter introduced by Husøy et al. [36] and used four reference signals to model the artifact: the thoracic impedance, the ECG common mode, the compression acceleration and the compression depth. Their database contained 184 shockable rhythms and 348 nonshockable rhythms randomly split into a training and a test set. After filtering, they obtained an excellent sensitivity of 96.7% but a low specificity of 79.9%.

Researchers then focused on reducing or eliminating the need for additional reference signals, in an effort to adapt these methods to a realistic AED scenario. (Some of these studies were based on the mixture model and are described in Section 3.1.) The Kalman filter based only on the ECG proposed by Ruiz de Gauna et al. [27] was tested on 131

shockable and 347 nonshockable rhythms extracted from the same original study used by Eilevstjønn et al. [14]. However, the overall results were poorer, 90.1% sensitivity and 80.4% specificity. Their results underlined the importance of using additional reference information to model the CPR artifact.

Using a dual-channel approach, Irusta et al. [15] proposed a CPR artifact model based on a time-varying Fourier series representation, which could be built using only the instantaneous frequency of the chest compressions. They obtained this frequency from the compression depth signal and adjusted the time-varying Fourier coefficients using a least mean squares (LMS) filter. The LMS filter was tested on 89 shockable and 292 nonshockable rhythms, with a sensitivity and specificity of 95.6% and 85.6%, respectively. Using this same database, Ruiz et al. [53] fitted the time-varying Fourier series model of the artifact by means of a Kalman filter. Furthermore, they conducted a spectral analysis of the rhythms and the CPR artifact and proved that the spectral overlap was larger for nonshockable rhythms, particularly for PEA. Aramendi et al. [28] showed that the instantaneous frequency used by the LMS filter could be derived from the thoracic impedance signal which is recorded by current AEDs through the defibrillation pads. This would eliminate the need of a chest device for acquiring additional reference signals. Finally, Ruiz de Gauna et al. [54] used an LMS finite impulse response filter to estimate the artifact using the force signal, in an effort to replicate the good results reported by Berger et al. [46] for a porcine model. The method was tested on 88 shockable and 292 nonshockable records; the sensitivity was 95.5% but the specificity after filtering was only 86.6%.

Tan et al. [29] introduced their artifact reduction and tolerant (ART) adaptive filter, which is currently integrated in a commercial AED (See-Thru CPR, ZOLL Medical), as a clinical support tool. Their adaptive filter is based on the CPR sternal velocity signal obtained by this particular AED from an accelerometer incorporated to the defibrillation pads which is placed beneath the rescuers hand. When tested on 114 shockable and 4155 nonshockable rhythms the method showed a sensitivity of 92.1% and a specificity of 90.5%.

In addition to adaptive filters, methods based on the direct analysis of the corrupted ECG have also been explored. In 2008, Li et al. [30] presented the first rhythm analysis method to directly diagnose the ECG corrupted by CPR artifacts, which was based on an ECG feature that is marginally affected by the artifact. This feature was obtained from the wavelet transform and the correlation function. The algorithm was validated with 1256 shockable and 964 nonshockable rhythms recorded from 229 OHCA patients during CPR, yielding a sensitivity of 93.3% and a specificity of 88.6%. Their method was proved to be more reliable for VF detection in the presence of CPR artifacts than several classical VF detection methods [55]. More recently, Krasteva et al. [31] presented a second method, this time based on features derived from the corrupted ECG and a reconstructed version of the ECG. After optimization, Krasteva et al. tested their algorithm on 172 shockable and 721 nonshockable rhythms obtained from 100 OHCA patients, for a sensitivity of 90.1% and a specificity of 86.1%.

Table 1 summarizes the results reported by six representative methods for rhythm analysis during CPR tested on human cardiac arrest data. The results cannot be directly compared for two reasons. First, the studies are based on different data, with very different prevalence of the rhythm types and different selection criteria for the rhythms. For example, these studies have large differences in the proportion of asystole among nonshockable rhythms, which may have important implications in the results given that asystole is the nonshockable rhythm with the largest prevalence [56] and the main cause of the low specificity [27]. Second, the studies based on adaptive filtering use different SAAs that may diagnose the filtered ECG differently. In fact, adaptive filters have been shown to have very similar sensitivities and specificities when tested using the same data and the same SAA [45, 57].

In any case, all these studies have some common limitations. Although the sensitivity is good, all studies present specificities well below the 95% recommended by the AHA. This would result in a large number of erroneous shock diagnoses during CPR, which would cause unnecessary CPR interruptions for nonshockable rhythms. In addition, these methods are evaluated using short rhythm intervals (10–20 s), which are sufficient for a shock/no-shock diagnosis and an evaluation of the method in terms of sensitivity and specificity. However, rhythm analysis during CPR is conceived to continuously diagnose the rhythm with the objective of improving CPR delivery compared to the standard CPR protocol, which requires interrupting CPR every two minutes for rhythm analysis. In this scenario the methods must be evaluated using long duration records, and a new methodology that goes beyond sensitivity/specificity for a single analysis is needed to quantify the effect of using these methods on the delivery of CPR. Over the last year, some studies have addressed and partially overcome these limitations. The following two sections describe these late advances in detail.

4. Rhythm Analysis during CPR: Impact on CPR Delivery

Current CPR guidelines recommend 2 minutes of uninterrupted CPR followed by a pause for rhythm reassessment [12, 13]. Rhythm analysis methods during CPR are conceived to improve CPR delivery compared to these recommendations. In this context, a rhythm analysis method would continuously analyze/monitor the rhythm during CPR with two objectives. First, advancing the shock to patients with shockable rhythms, which could be beneficial given the high oxygen demands of recurrent VF [58]. Second, prolong uninterrupted CPR beyond two minutes for patients with nonshockable rhythms, therefore increasing the chest compression fraction which increases the likelihood of ROSC [11].

In 2005, Eilevstjønn et al. [59] proposed a set of modifications in AED operation to potentially reduce no-flow times (NFT), which is equivalent to increasing the chest compression fraction. These modifications included continuous

Table 1: Comparison of six different approaches to rhythm analysis during CPR tested on OHCA registers. The confidence intervals for sensitivity (Se) and specificity (Sp) were computed using Wald's interval for binomial proportions. For the number of nonshockable rhythms the proportion is indicated in parenthesis, and NA stands for not available.

Authors	Method	Se (%)	Sp (%)	Testing datasets	
				S	NS
Eilevstjønn et al. [14]	MC-RAMP	96.7 (87.6–98.0)	79.9 (73.3–85.2)	92	174 (30%)
Ruiz de Gauna et al. [27]	Kalman filter	90.1 (83.6–94.2)	80.4 (75.9–84.3)	131	347 (43%)
Aramendi et al. [28]	LMS filter	95.4 (88.4–98.6)	86.3 (81.8–89.9)	87	285 (31%)
Tan et al. [29]	ART filter	92.1 (86.8–95.5)	90.5 (89.7–91.2)	114	4155 (NA)
Li et al. [30]	Direct analysis	93.3 (92.0–94.4)	88.6 (86.8–90.2)	1256	964 (4%)
Krasteva et al. [31]	Direct analysis	90.1 (85.6–94.6)	86.1 (83.6–88.7)	172	721 (46%)

rhythm analysis during CPR and, in the event of a shockable rhythm, a short hands-off period for rhythm verification in which the capacitor would also be charged. In addition, they proposed 1 min of uninterrupted CPR immediately after a shock and rhythm analysis during CPR starting after that minute. They analyzed 105 complete resuscitation episodes and concluded that the median NFT could be theoretically reduced from 51% to 34% and from 49% to 39% for patients in shockable and nonshockable rhythms, respectively. Eilevstjønn et al. did not consider the impact of misdiagnosing the rhythm during chest compressions in their estimations of the potential reduction in NFT. However, errors in diagnosis would be frequent given the low specificity of current methods. Consequently, the real impact on CPR delivery of continuous rhythm analysis was not assessed.

Ruiz et al. [24] recently introduced a methodology to evaluate the real impact of rhythm analysis methods on CPR delivery. The methodology is based on the evaluation scenario described in Figure 6. This scenario starts with 1 minute of uninterrupted CPR, as introduced by Eilevstjønn et al. [59], to guarantee a minimum period of blood flow. Then rhythm analysis during CPR starts and CPR continues until a shock is advised. In this scenario, the time to the first shock diagnosis determines the duration of the uninterrupted CPR time (t_{uCPR}). For an adaptive filter followed by a SAA, Ruiz et al. computed t_{uCPR} on 242 shockable and 634 nonshockable long duration OHCA segments. Then they estimated the probability of interrupting CPR as a function of time using Kaplan-Meier survival curves for both shockable and nonshockable rhythms.

The rhythm analysis method had a sensitivity of 94% and specificity of 81%, that is, an accuracy comparable to those reported in the literature. However the estimated impact on CPR delivery was much larger than anticipated. Although 100% of patients in shockable rhythms would receive a shock earlier, CPR would be interrupted before 2 minutes in 42% of patients in nonshockable rhythms. This would reduce the chest compression fraction in a large number of cases resulting in a compromised probability of survival.

Methodologically, the study by Ruiz et al. starts a new stage in rhythm analysis during CPR centered on evaluating the effects on CPR delivery of using these methods. Their results confirm and amplify a well known problem; the specificity of current methods is still too low. However, the impact of the low specificity on CPR delivery is much larger than anticipated. New strategies to reduce interruptions in CPR delivery are needed.

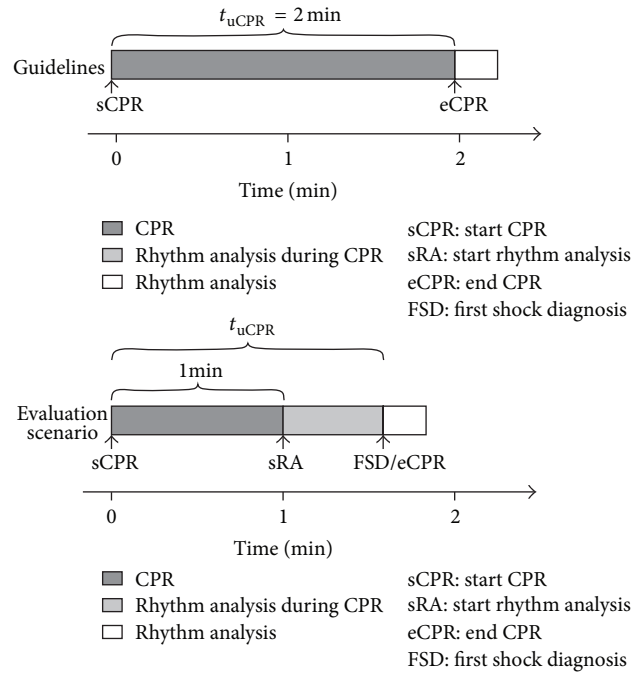
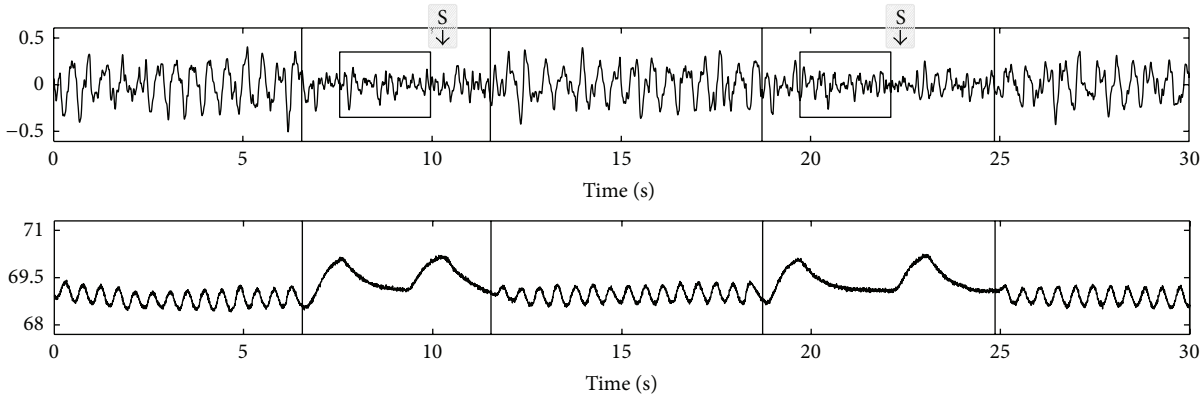


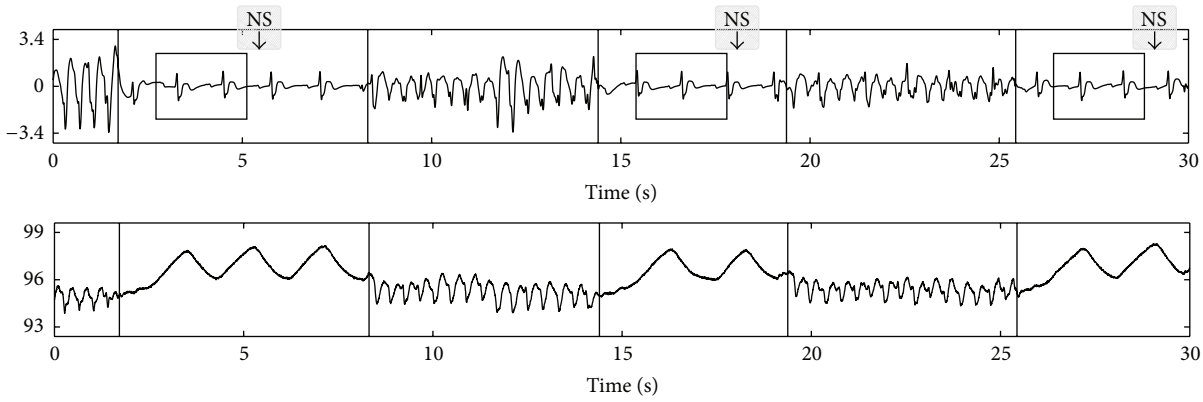
Figure 6: Evaluation scenario proposed by Ruiz et al. [24] for continuous rhythm analysis during CPR, which consists of 1 minute of uninterrupted CPR followed by rhythm analysis during CPR. CPR stops when the rhythm analysis method gives the first shock diagnosis. The t_{uCPR} obtained in this manner is then compared to the guideline's recommendation of 2 minutes of t_{uCPR} after a shock or a pause for rhythm reassessment. The figure has been adapted from Ruiz et al. [24].

5. New Strategies to Rhythm Analysis during CPR

To date, the methods for rhythm analysis during CPR have focused mainly on two key ideas: (1) analyzing the rhythm during chest compressions and (2) prioritizing the detection



(a) Rhythm analysis during the ventilation pauses for a patient in VF



(b) Rhythm analysis during the ventilation pauses for a patient in PEA

Figure 7: Examples of rhythm analysis during the ventilation pauses; in both examples the top panels show the ECG in mV and the lower panel shows the thoracic impedance in Ω. In the impedance channel chest compression artifacts (fast fluctuations) and ventilation artifacts (slow fluctuations) are visible. During the pauses for ventilation there are no chest compression artifacts in the ECG and the high temporal-resolution SAA gives an accurate diagnosis using 3 s windows. The examples have been adapted from Ruiz et al. [25].

of shockable records above the detection of nonshockable records. Unfortunately the accuracy of the methods has not improved much over these last years. Consequently, some recent efforts have started to explore new strategies for rhythm analysis during CPR.

5.1. Rhythm Analysis during Chest Compression Pauses. Before tracheal intubation current resuscitation guidelines recommend a 30 : 2 compression to ventilation (CV) ratio for CPR. Each cycle of 30 chest compressions, which at the standard rates takes approximately 18 s, is followed by a pause for two rescue breaths. Although the guidelines limit the time for two rescue breaths to 5 s, in real practice the median pause duration is 7 s [60]. During ventilations there are no visible artifacts that may affect rhythm analysis, as shown in Figure 7. Based on this premise, Ruiz et al. [25] proved that it was possible to analyze the rhythm during chest compression pauses, ventilation or nonventilation pauses, using a high temporal-resolution SAA, that is, an algorithm capable of giving an accurate diagnosis in 3 s [26]. Figure 7 illustrates this method for a shockable and a nonshockable rhythm. They analyzed 110 shockable and 466 nonshockable long duration OHCA segments and manually identified a total of 4476 pauses in chest compressions, of which 2183 were ventilation pauses with two rescue breaths. The pauses had a median duration of 6.1 s, 5.5 s for those with two rescue breaths, and 91% of all the pauses and 95% of the ventilation pauses with two breaths were longer than 3 s, which made them suitable for a rhythm analysis by the SAA. The sensitivity and specificity were 95.8% and 96.8%, respectively, well above the AHA recommendations.

A key component to incorporate this solution into a defibrillator is the automatic identification of the intervals without chest compressions. Depending on the available equipment, different reference channels could be used for this purpose. In a scenario with an external CPR assist device the identification could be performed using the compression depth or the force channels. However, most defibrillators do not incorporate this technology, so a more general solution based on the impedance signal should be explored. Pauses in chest compressions [61], ventilations [62], and the end of chest compressions [63] have already been detected on the impedance, although a complete valid system has not yet been demonstrated.

Devices incorporating this solution would have an accurate rhythm analysis approximately every 18 s for CPR delivered at a 30 : 2 CV ratio for a standard compression rate of 100 cpm. The AED could then guide therapy using this feedback to monitor nonshockable rhythms or for early recognition of recurrent VF, converting AEDs into intelligent devices.

5.2. Rhythm Analysis during Chest Compressions. In the last years there has been an increasing debate about the need for active ventilations during CPR. Several studies have shown an increased survival rate when compression only CPR (COCPR) was administered compared with the standard 30 : 2 CV ratio CPR [64, 65]. In the future resuscitation guidelines may recommend COCPR. In fact, current guidelines state that COCPR may be used by untrained bystanders or bystanders unwilling to give rescue breaths [12, 13]. In this scenario, new and reliable methods to analyze the rhythm during chest compressions should be developed.

As shown in Section 4, in a continuous rhythm analysis scenario CPR would only be stopped when a shock is advised. If the patient presents a shockable rhythm, an erroneous no-shock diagnosis could be corrected in the upcoming rhythm analyses if the sensitivity of the method is not too low. On the other hand, for patients in nonshockable rhythms a single erroneous shock diagnosis entails an unnecessary CPR interruption. Consequently, efforts should focus on increasing the specificity. Based on our 10-year experience on this field, we believe that the following three strategies should be explored and combined.

(1) From a SAA design perspective the accuracy of the method could be increased by merging the two most successful strategies for rhythm analysis during CPR: adaptive filters to suppress the CPR artifact combined with rhythm analysis algorithms designed to work during CPR. Although adaptive filters substantially reduce the CPR artifact, with SNR improvements of up to 35 dB [29], a filtering residual always remains. These residuals frequently resemble a disorganized rhythm [14, 15, 53] and may produce a shock diagnosis in SAAs designed for artifact free ECGs. This is particularly severe when the underlying nonshockable rhythm has low electrical activity like during asytole or low rate PEA. SAAs designed to analyze the ECG in the presence of filtering residuals should be designed with emphasis on increasing the specificity.

(2) Sometimes the chest compression artifact is so large that even state of the art adaptive filters cannot effectively eliminate it. In these cases the rhythm analysis following filtering is grossly equivalent to a coin toss. However, if the rhythm is continuously analyzed these unreliable analyses can be safely ignored until the amplitude of the artifact decreases. SAAs could add a block before rhythm analysis to identify large chest compression artifacts and wait until a safe rhythm analysis is possible.

(3) The confidence in a shock decision could be further increased by efficiently combining several rhythm analysis decisions. For instance, instead of using a shock/no-shock decision per analysis window, the algorithm could return an estimate of the probability of having a shockable rhythm. In a continuous rhythm analysis scenario several of these probabilities could be conservatively combined before a shock is actually decided.

Rhythm analysis during CPR could be further enhanced if these strategies were combined with techniques to determine the optimal time for shock delivery. In the past 20 years, considerable efforts have been made on VF waveform analysis to define predictors of defibrillation success and outcome such as median slope [66], scaling exponent [67], and amplitude Spectrum Analysis (AMSA) [68, 69]. Incorporating rhythm analysis during CPR and assessment of the optimal time to defibrillate would lead to a new generation of intelligent AEDs, capable of guiding therapy individually.

Finally, rhythm analysis methods during chest compressions should be evaluated in terms of their impact on CPR delivery, as described in Section 4. Ruiz et al. [24] proposed that for nonshockable rhythms these methods should guarantee a probability greater than 95% of delivering at least 2 minutes of uninterrupted CPR (meet guidelines) and a probability greater than 90% of delivering at least 3 minutes of uninterrupted CPR (improve chest compression fraction compared to guidelines). In addition, they should guarantee that the shock is advanced in at least 90% of shockable rhythms. Although these recommendations seem reasonable, they should be appraised by the resuscitation research community.

6. Conclusions

Currently, there is insufficient evidence to support or refute the use of algorithms for rhythm analysis during CPR. The evaluation of these algorithms in terms of sensitivity and specificity on short ECG segments does not accurately predict their impact on CPR delivery. As stated by the CoSTR, studies must demonstrate that rhythm analysis during CPR optimizes the time of appropriate chest compressions. To this aim, the probability of interrupting CPR as a function of time has been proposed as a new evaluation figure. In this new framework, the classical sensitivity/specificity goals would change to new goals for uninterrupted CPR time.

Recently, new solutions have been proposed for rhythm analysis during CPR. Hands-off intervals for rhythm analysis could be completely eliminated by assessing the rhythm during ventilation pauses using a high temporal-resolution SAA. On the other hand, accurate SAAs with high specificity should be designed to work during chest compressions for COCPR scenarios. Retrospective studies with large databases of complete OHCA episodes should be conducted to simulate continuous rhythm analysis and measure the impact on CPR delivery. Later, prospective studies using defibrillators incorporating these algorithms could definitely prove if survival improves.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Outcome of Prolonged Ventricular Fibrillation and CPR in a Rat Model of Chronic Ischemic Left Ventricular Dysfunction

Xiangshao Fang,[1,2] Lei Huang,[2] Shijie Sun,[2,3] Max Harry Weil,[2,3] and Wanchun Tang[1,2,3]

[1] *Department of Emergency Medicine, Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Guangzhou, Guangdong 510120, China*
[2] *Weil Institute of Critical Care Medicine, Rancho Mirage, CA 92270, USA*
[3] *The Keck School of Medicine of the University of Southern California, Los Angeles, CA 90033, USA*

Correspondence should be addressed to Xiangshao Fang; fxshao@hotmail.com

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Patients with chronic left ventricular (LV) dysfunction are assumed to have a lower chance of successful CPR and lower likelihood of ultimate survival. However, these assumptions have rarely been documented. Therefore, we investigated the outcome of prolonged ventricular fibrillation (VF) and CPR in a rat model of chronic LV dysfunction. Sprague-Dawley rats were randomized to (1) chronic LV dysfunction: animals underwent left coronary artery ligation; and (2) sham control. Echocardiography was used to measure cardiac performance before surgery and 4 weeks after surgery. Four weeks after surgical intervention, 8 min of VF was induced and defibrillation was delivered after 8 min of CPR. LV dilation and low ejection fraction were observed 4 weeks after coronary ligation. With optimal chest compressions, coronary perfusion pressure values during CPR were well maintained and indistinguishable between groups. There were no differences in resuscitability and numbers of shock required for successful resuscitation between groups. Despite the significantly decreased cardiac index in LV dysfunction animals before induction of VF, no differences in cardiac index were observed between groups following resuscitation, which was associated with the insignificant difference in postresuscitation survival. In conclusion, the outcomes of CPR were not compromised by the preexisting chronic LV dysfunction.

1. Introduction

A majority of episodes of sudden cardiac deaths occur in victims with ischemic heart disease. Ischemic heart disease may develop over a lengthy span of time and is often associated with left ventricular (LV) remodeling. This ultimately leads to chronic ischemic LV dysfunction with subsequent congestive heart failure. Lower ejection fraction (EF) has been consistently demonstrated to be the strongest independent predictor of sudden cardiac death [1–3]. When cardiac arrest occurs in patients with chronic ischemic LV dysfunction, they are assumed to have a lower chance of successful cardiopulmonary resuscitation (CPR) and lower likelihood of ultimate survival. However, these assumptions have rarely been documented. Little is known about prognostic information concerning the outcomes of CPR in patients with chronic ischemic LV dysfunction.

The goals of the present study were therefore to obtain prognostic information on the outcome of prolonged ventricular fibrillation (VF) and CPR in the chronic ischemic LV dysfunction due to complete left coronary artery ligation in Sprague-Dawley rats. We hypothesized that when undergoing prolonged VF/CPR, chronic ischemic LV dysfunction animals would be less likely to be resuscitated. If resuscitated, such animals would be likely to have more severe postresuscitation myocardial dysfunction and decreased duration of postresuscitation survival.

2. Materials and Methods

This study was approved by the Institutional Animal Care and Use Committee of the Weil Institute of Critical Care Medicine. All animals received humane care in compliance with the *Principles of Laboratory Animal Care* formulated by the National Society for Medical Research and the *Guide for the Care and Use of Laboratory Animals* prepared by the Institute of Laboratory Animal Resources and published by the National Institutes of Health.

2.1. Study Design. Fourteen male Sprague-Dawley rats weighing 500 ± 50 g were randomized into (1) chronic ischemic LV dysfunction group ($n = 7$): the animals underwent left coronary artery ligation 4 weeks before induction of VF; and (2) control group ($n = 7$). The animals received sham operation without coronary artery ligation 4 weeks before induction of VF.

2.2. Chronic Ischemic LV Dysfunction Model. The animals were fasted overnight except for free access to water. They were anesthetized by intraperitoneal injection of pentobarbital (45 mg/kg). The animals were then orally intubated and mechanically ventilated with room air. Electrocardiogram (ECG) was continuously monitored. After measurements of baseline myocardial function using noninvasive transthoracic echocardiography, a thoracotomy via the third left intercostal space was performed. The atrial appendage was elevated and the left coronary artery near its origin was ligated. Successful ligation was confirmed by the ST segment elevation. The chests were then closed, and the animals were returned to their cages. Postsurgical pain was controlled with intramuscular injection of ketorolac (0.4 mg/kg). Control rats were prepared similarly except that the coronary artery was not ligated.

2.3. Experimental Procedures of VF/CPR. Four weeks after surgical intervention, the animals were reanesthetized and intubated. Cardiac geometry and function were assessed by echocardiography. A PE-50 catheter (Becton Dickinson) was advanced from the right carotid artery into the left ventricle for measurement of LV pressure. A PE-50 catheter was advanced through the left external jugular vein into the right atrium for measurement of right atrial pressure. For electrical induction of VF, a 4 French PE catheter was advanced through the right external jugular vein into the right atrium, and through its lumen a precurved guide wire was then advanced into the right ventricle for electrically inducing VF. A PE-50 catheter was advanced through the left femoral artery into the thoracic aorta for measurement of mean aortic pressure (MAP). A thermocouple microprobe (9030-12-D-34, Columbus Instruments; Columbus, OH) was advanced from the right femoral artery into the descending thoracic aorta for measurement of blood temperature. ECG was recorded. A heat lamp was used to maintain body temperature at 36.8°C (±0.2%).

The animals were mechanically ventilated with room air at a tidal volume of 0.55 mL/100 g and a frequency of 100 breaths/min. A progressive increase in 60 Hz current to a maximum of 4 mA was then delivered to the right ventricular endocardium. The current flow was continued for 3 min to preclude spontaneous reversal of VF. Mechanical ventilation was discontinued after onset of VF. Precordial compression was then begun and mechanical ventilation with 100% O_2 was resumed 8 min after the onset of VF. Precordial compression at a rate of 200 min^{-1} was synchronized to provide a compression/ventilation ratio of 2 : 1. The depth of compression was adjusted to maintain a coronary perfusion pressure (CPP) at 24 ± 2 mmHg. Resuscitation was attempted with up to three 2-J biphasic waveform countershocks (CodeMaster XL, Heartstream Operation, Philips; Seattle, WA) after 8 min of CPR. Return of spontaneous circulation (ROSC) was defined as an organized rhythm with MAP ≥60 mmHg for ≥5 min.

Following ROSC, the animals were monitored for 4 hours. All catheters were then removed. The animals were observed for an additional 68 hours after which they were euthanized with an intraperitoneal injection of pentobarbital sodium (150 mg/kg). An autopsy was performed to confirm the complete ligation of left coronary artery, and organs were inspected for gross abnormalities, including evidence of traumatic injuries consequent to cannulation, airway management, or precordial compression.

2.4. Measurements. LV geometry and cardiac function prior to and 4 weeks after ligation was quantitated with a Sonos 2500 echocardiographic system utilizing a 7.5 Hz transducer (Model 21363A, Hewlett-Packard Co., Medical Products Group, Andover, MA). The animal hearts were imaged in the parasternal short-axis plane through the anterior chest. At two-dimensional imaging of short-axis view, left ventricular end-systolic volumes (LVESV) and left ventricular end-diastolic volumes (LVEDV) were calculated by the method of discs (Acoustic Quantification Technology, Hewlett-Packard, Andover, MA). From these, EF was computed.

Aortic, LV, right atrial pressures, and ECG were recorded via a WinDaqdata-acquisition system (DataQ; Akron, OH). CPP was calculated as the difference between aortic and time-coincident right atrial pressures in the interval between chest compressions.

Myocardial function during VF/CPR experimental phase was assessed from measurements of LV pressure and cardiac output. The rate of LV pressure increase at 40 mmHg (dP/dt_{40}) was measured by analog differentiation as an indicator of isovolumic contractility. The rate of LV pressure decline ($-dP/dt$) was measured as an indicator of myocardial relaxation. Cardiac output was measured by a thermodilution technique with the aid of a cardiac-output computer fabricated at our institute. The data were reported as cardiac index (CI) values as an indicator of global pump function.

2.5. Analyses. Measurements are reported as means ± SD. Comparisons between groups before surgical operation and 4 weeks after coronary ligation were performed by using Student's t-test. Following ROSC, comparisons between time-based measurements within each group were performed with analysis of variance for repeated measurements. The success of resuscitation and 72-hour survival rate were analyzed with Fisher's exact test. Survival analysis was performed with the Kaplan-Meier method. A value of $P < 0.05$ was regarded as significant.

3. Results

Before surgical operations, there were no differences in baseline values of echocardiographically measured LVEDV, LVESV, and EF between groups (Figure 1). Significant decreases in EF and increases in LVEDV and LVESV were

Table 1: Effects of intervention on ROSC, number of 72-hour survival, and number of defibrillations.

Group	ROSC	72-hour survival	Number of shocks
Chronic LV dysfunction	6/7	3/6	1.2 ± 0.4
Control	5/7	3/5	1.4 ± 0.9

Values are means ± SD. ROSC: return of spontaneous circulation.

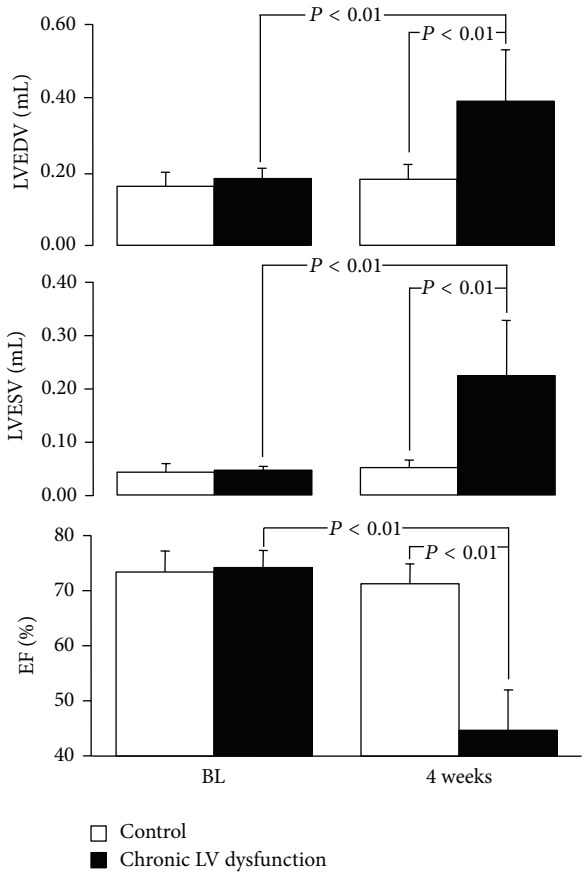

Figure 1: Echocardiographic measurements at baseline (BL) and 4 weeks after left coronary artery ligation. Values are means ± SD. LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; EF: ejection fraction.

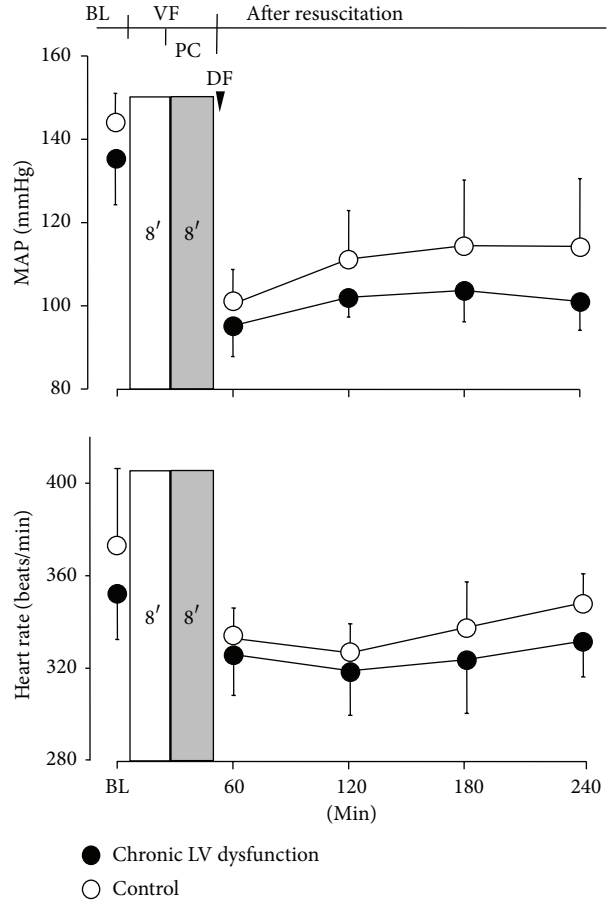

Figure 2: Mean aortic pressure and heart rate before onset of cardiac arrest and following resuscitation. Values are means ± SD. MAP: mean aortic pressure; BL: baseline; VF: ventricular fibrillation; PC: precordial compression; DF: defibrillation.

documented in chronic ischemic LV dysfunction animals 4 weeks after coronary ligation.

CPP values were maintained at 24 ± 2 mmHg for all animals during the entire period of CPR. There were no differences in resuscitability and total shock energy required for ROSC between groups (Table 1).

Before induction of VF and following ROSC, there were no significant differences in both MAP and heart rate in heart failed animals when compared with control animals (Figure 2).

Myocardial function, as measured by dP/dt_{40} and $-dP/dt$, was significantly decreased in LV dysfunction animals before induction of VF and over 4 hours after resuscitation compared with control animals (Figure 3). Similarly, LV end-diastolic pressure (LVDP) was significantly increased in LV dysfunction animals at baseline before induction of VF and following ROSC compared with control animals (Figure 4). Four weeks after coronary ligation but prior to induction of VF, the resting CI in LV dysfunction animals was significantly lower than that of control animals. However, no significant difference in CI was observed between groups following resuscitation (Figure 5). No differences in the number of animals surviving 72 hours and duration of survival (survival curve) were observed between groups (Table 1; Figure 6).

At autopsy, transmural scar formation of the LV anterior wall was observed in LV dysfunction animals. No gross abnormalities were observed at autopsy in any animals.

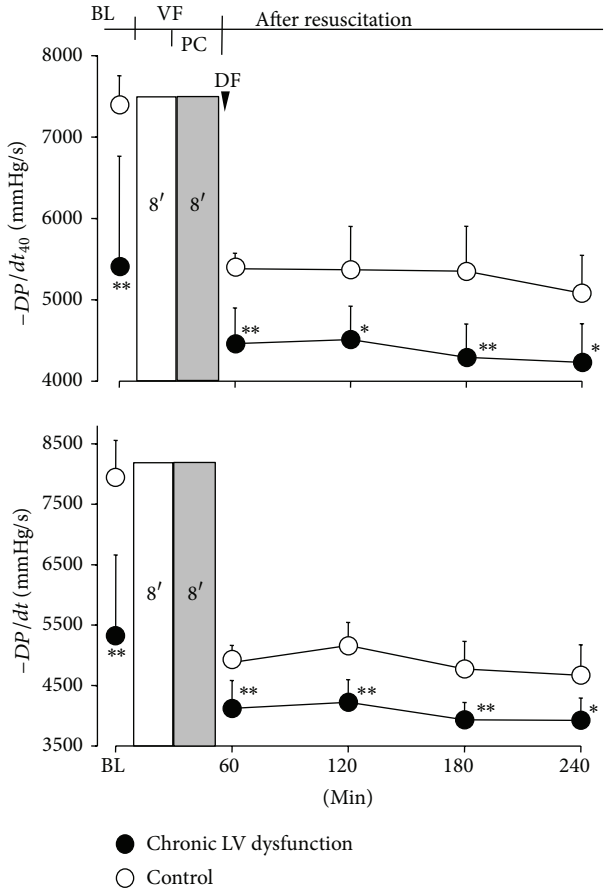

Figure 3: dP/dt_{40} and $-dP/dt$ before onset of cardiac arrest and following resuscitation. Values are means ± SD; $^{*}P < 0.05$; $^{**}P < 0.01$ versus control. BL: baseline; VF: ventricular fibrillation; PC: precordial compression; DF: defibrillation.

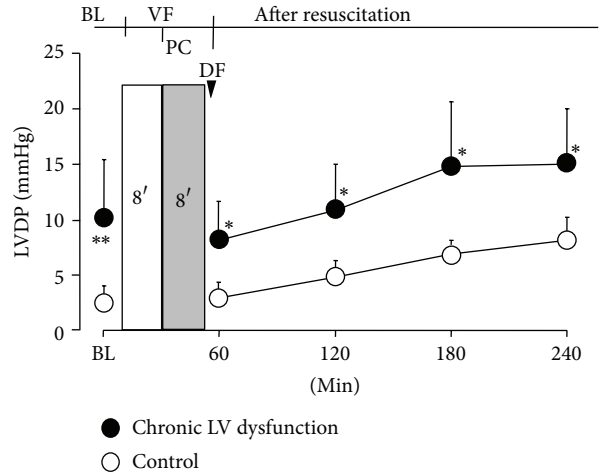

Figure 4: LV end-diastolic pressure (LVDP) before onset of cardiac arrest and following resuscitation. Values are means ± SD; $^{*}P < 0.05$; $^{**}P < 0.01$ versus control. BL: baseline; VF: ventricular fibrillation; PC: precordial compression; DF: defibrillation.

4. Discussion

In this study, CPR was performed effectively after prolonged VF in a rat model of chronic ischemic LV dysfunction. With optimal chest compressions, the ease of defibrillation and cardiac resuscitability were not compromised by the preexisting chronic LV dysfunction. Furthermore, this study revealed that it was the systemic blood that flows through the circulation following ROSC, rather than the preexisting chronic LV dysfunction, which was the predominant determinant of postresuscitation survival.

Fewer studies have directly evaluated the influence of preexisting chronic ischemic LV dysfunction on the likelihood of resuscitability and ultimate postresuscitation survival. Previously we have demonstrated the feasibility of applying CPR in a rat model of chronic nonocclusive left coronary artery constriction [4]. It is unexpected to notice that no differences in resuscitability and postresuscitation short-term outcome were observed between coronary constriction animals and control animals. We suppose that this may be due to the possibilities that heart function is less impaired after coronary artery narrowing and that downtime of VF/CPR is too short to differentiate the effects of myocardial ischemia on the survival outcome [4]. The goals of the present study were therefore to obtain prognostic information on the outcome of prolonged VF/CPR in chronic ischemic LV dysfunction due to left coronary artery complete ligation.

Overt LV dysfunction and extensive ventricular remodeling were observed in left coronary artery ligation animals. Myocardial function as assessed by EF, CI, dP/dt_{40}, and $-dP/dt$ was significantly depressed and LVDP was significantly increased 4 weeks after coronary ligation. The LV remodeling was manifested by the significantly larger LVEDV and LVESV. Taken together, our results suggested the severe deterioration in LV pump dynamics and extensive ventricular remodeling in this rat model.

In the current study, the number of defibrillations and resuscitability in LV dysfunction animals did not differ from thoat in control. It is well known that the myocardial blood flow is the overriding determinant for the success of resuscitation effort, especially when the duration of untreated cardiac arrest is prolonged [5, 6]. It has also been suggested that CPP correlates well with myocardial blood flow [7–9] and has served as the most reliable quantitative predictor of the success of resuscitation in experimental models and in human patients [10, 11]. Following the prolonged period of untreated cardiac arrest, the rationale of chest compression is to rapidly restore threshold levels of CPP and, therefore, myocardial blood flow. In the present study, all animals were submitted to identical qualities of external chest compressions and mechanical ventilations. The fact that CPP values during CPR were comparable between groups demonstrated that the qualities of chest compressions were well controlled for all animals. Our findings therefore suggested that the ease of defibrillation and resuscitability are not diminished by the preexisting chronic LV dysfunction but largely determined by the quality of CPR efforts.

Following ROSC, the primary goal of patient care is to ensure that the patient has adequate spontaneous circulation,

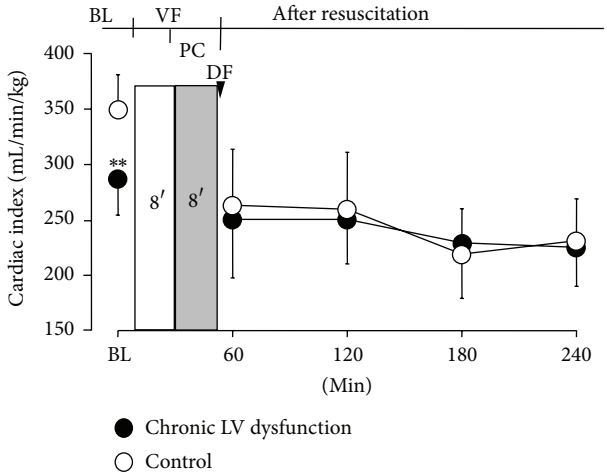

Figure 5: Cardiac index before onset of cardiac arrest and following resuscitation. Values are means ± SD; $^{**}P < 0.01$ versus control. BL: baseline; VF: ventricular fibrillation; PC: precordial compression; DF: defibrillation.

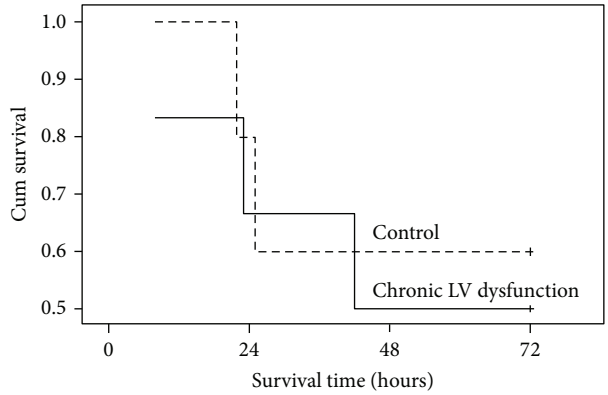

Figure 6: Kaplan-Meier survival curves.

such that the whole-body ischemia/reperfusion injury can be prevented, minimized, or reversed; subsequently, the ultimate postresuscitation survival with intact organ function might be improved. Reversible myocardial dysfunction has been observed after ROSC in experimental models [12] and in human patients [13, 14]. This dysfunction may result in acute hemodynamic compromise leading to profound hypoperfusion that adds additional ischemic injury to vital organs, and has been associated with early death after initial successful resuscitation [15]. In the present investigation, myocardial contractile dysfunction as assessed by decreased dP/dt_{40} and CI and diastolic dysfunction assessed by decreased $-dP/dt$ were observed in all animals after resuscitation. Among these standard measurements, the index of resting CI represents global blood flow through the entire systemic circulation to vital organs. The positive correlation between CI and duration of postresuscitation survival has previously been demonstrated by us in a rodent model of VF/CPR [16, 17]. These observations indicated that inadequate systemic blood flow was associated with poor postresuscitation survival. In the present investigation, the fact that there was no difference in postresuscitation CI between groups suggested the comparable global organ blood flow after resuscitation. These may in part explain the insignificant difference in duration of postresuscitation survival between groups.

It is interesting to notice that no difference in CI following ROSC was observed between groups regardless of the significant difference before induction of VF. Previously the phenomenon of adaptive process of chronic hypoxia conferring myocardial tolerance to subsequent acute severe hypoxia/reoxygenation or ischemia/reperfusion injury has been observed in cardiac myocytes models [18, 19] and isolated perfused heart models [20]. Such observations have been supported by clinical investigation of coronary artery bypass surgery [21], in which investigators found that similar severity of ischemia/reperfusion induced moderate overall ultrastructural changes in normally contracting myocardium whereas only minor overall ultrastructural changes in postreperfusion hibernating myocardium. Similar to these observations, our work suggested that chronic heart failure might increase myocardial ischemic tolerance against impending insult of VF/CPR, which was manifested as the insignificant difference in postresuscitation CI, and subsequently the insignificant difference in postresuscitation survival between groups.

There are limitations that need to be acknowledged and addressed regarding the present study. Clinically, most episodes of VF are caused by ischemic heart disease rather than electric shock. We recognized that despite the minimal level of current flow, the potential electrical injury to the myocardium would likely compromise the clinical relevance of this rat model of VF/CPR. Regardless of this potential shortcoming, this, however, did not alter our conclusion since all the animals receive the same procedure. In this preliminary study, CPP is adopted as a reflection of myocardial blood flow. We admitted that ideally myocardial blood flow should be measured by real-time techniques during CPR and following resuscitation. However, aiming to observe the effect of chronic ischemic LV dysfunction on the duration of postresuscitation survival and the technical difficulties of directly measuring myocardial blood flow during chest compressions do not enable us to perform such measurement in real time. Nevertheless, based on the current data, we cautiously draw the conclusion that the extent of levels of CPP can, in part, reflect myocardial blood flow. In addition, we admit that our current studies lack direct evidence about the underlying mechanisms responsible for the phenomenon of "myocardial ischemic tolerance to insult of cardiac arrest and CPR." This relatively preserved postresuscitation myocardial function in the chronic ischemic heart deserves further investigation. Finally, we admit that LVEF values before induction of VF are greater than those we usually observed in patients with chronic heart failure. Nevertheless, we do observe that the outcomes of CPR were not compromised by preexisting chronic ischemic LV dysfunction. The appropriate animal model and optimal experimental design will be considered in our future investigations, so that the effect of more depressed LVEF on the outcome of CPR can be further revealed.

Our findings may have potential clinical implications. First, our work indicates that efficacy of chest compressions during CPR overrides the detrimental effect of preexisting chronic heart failure in determining the likelihood of successful resuscitation. Second, since postresuscitation outcome was largely determined by the systemic blood flow, the postresuscitation patient care should be focused on maintaining and improving global blood flow following resuscitation, such that the ultimate postresuscitation survival with intact organ function might be improved.

Abbreviations

CI: Cardiac index
CPP: Coronary perfusion pressure
CPR: Cardiopulmonary resuscitation
EF: Ejection fraction
LV: Left ventricular
LVDP: Left ventricular end-diastolic pressure
LVESV: Left ventricular end-systolic volume
LVEDV: Left ventricular end-diastolic volume
MAP: Mean aortic pressure
ROSC: Return of spontaneous circulation
VF: Ventricular fibrillation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

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Research Article

Improved Early Postresuscitation EEG Activity for Animals Treated with Hypothermia Predicted 96 hr Neurological Outcome and Survival in a Rat Model of Cardiac Arrest

Bihua Chen,[1] Feng-Qing Song,[2] Lei-Lei Sun,[2] Ling-Yan Lei,[2] Wei-Ni Gan,[2] Meng-Hua Chen,[2] and Yongqin Li[1]

[1] *School of Biomedical Engineering, Third Military Medical University and Chongqing University, Chongqing 400038, China*
[2] *Institute of Cardiovascular Diseases, The First Affiliated Hospital of Guangxi Medical University, Nanning 530021, China*

Correspondence should be addressed to Yongqin Li; leeoken@gmail.com

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Purpose. To investigate the effect of hypothermia on 96 hr neurological outcome and survival by quantitatively characterizing early postresuscitation EEG in a rat model of cardiac arrest. *Materials and Methods.* In twenty male Sprague-Dawley rats, cardiac arrest was induced through high frequency transesophageal cardiac pacing. Cardiopulmonary resuscitation was initiated after 5 mins untreated arrest. Immediately after resuscitation, animals were randomized to either 2 hrs of hypothermia ($N = 10$) or normothermia ($N = 10$). EEG, ECG, aortic pressure, and core temperature were continuously recorded for 6 hrs. Neurological outcome was evaluated daily during the 96 hrs postresuscitation period. *Results.* No differences in the baseline measurements and resuscitation outcome were observed between groups. However, 96 hr neurological deficit score (204 ± 255 versus 500 ± 0, $P = 0.005$) and survival (6/10 versus 0/10, $P = 0.011$) were significantly better in the hypothermic group. Quantitative analysis of early postresuscitation EEG revealed that burst frequency and spectrum entropy were greatly improved in the hypothermic group and correlated with 96 hr neurological outcome and survival. *Conclusion.* The improved burst frequency during burst suppression period and preserved spectrum entropy after restoration of continuous background EEG activity for animals treated with hypothermia predicted favorable neurological outcome and survival in this rat model of cardiac arrest.

1. Introduction

Out-of-hospital cardiac arrest (CA) is a major public health problem all over the world. Each year, an estimated 325,000 victims in USA, 350,000 in Europe, and 544,000 in China suffer out-of-hospital CA [1–3]. Despite efforts to improve outcomes from CA, the overall survival is less than 10% among patients successfully resuscitated [4, 5]. In patients who achieved return of spontaneous circulation (ROSC), the resulting anoxic ischemia brain injury is a major cause of morbidity and mortality [6, 7]. The greatest postresuscitation emphasis has mainly been on preserving neurologic function [8].

Among all postresuscitation care suggested and/or recommended, therapeutic hypothermia (TH) is the most persuasive intervention that can significantly improve neurologic recovery and survival after resuscitation from CA [9, 10]. However, patient selection and the optimization of postarrest hypothermia treatment remain problematic issues because there are no clinically validated tools to determine who might benefit from the therapy, how long hypothermia should be conducted, and how to avoid/reduce occurrence of complications [9, 10]. Early prediction of outcome may be, in fact, an important aspect to be considered during the postresuscitation care in order to avoid the likelihood of unnecessary prolongation of TH when a good functional recovery has already been achieved or to avoid unjustified withdrawal of care if the protection has not been fully achieved yet. For years, neurological examination and electrophysiological studies have guided physicians in predicting

outcome in comatose survivors of CA, including pupillary light response, serum neuron-specific enolase, somatosensory evoked potentials, and combinations thereof [11–14]. But early prognostication remains challenging, especially because the predictive values of clinical, biochemical, and electrophysiological variables have become uncertain after the introduction of TH [15–17].

The electroencephalogram (EEG), which reflects part of the function of cortical neurons, is very sensitive to ischemia. Previous studies found that EEG burst characteristics were associated with neurological recovery in animal model of CA from asphyxia [18, 19]. At the same time, observational clinical studies reported that persistence of isoelectric activity, burst suppression, or generalized epileptiform discharges on EEG was associated with poor outcomes [20–23]. Although unprocessed EEG interpretation observed during the early stage after resuscitation has been used to assist the prediction of a poor outcome in comatose survivors without hypothermia with some success, the prognostic accuracy was insufficient, especially in the era of hypothermia [24–27]. Meanwhile, the EEG literatures of clinical study are confounded by different classification systems, causes of CA, arrest time, duration of cardiopulmonary resuscitation (CPR), medications used, and intervals of recordings after resuscitation [28]. The characteristics of EEG during early postresuscitation period and the effect of hypothermia on EEG recovery and its prognostication value are still unclear [9, 10, 28].

In the present study, we investigated the effect of mild hypothermia on EEG recovery, as well as the relationship between characteristics of early postresuscitation EEG activities and 96 hr neurological outcome and survival in a rat model of CA.

2. Materials and Methods

This study was approved by the ethics of animal investigation committee of Guangxi Medical University. All animals received humane care in compliance with the Principles of Laboratory Animal Care and Guide for the Care and Use of Laboratory Animals [29].

2.1. Animal Preparation. Twenty male Sprague-Dawley rats weighing 230 to 334 g were fasted overnight but had free access to water. Anesthesia was initiated by intramuscular injection of (0.3 g/kg) chloral hydrate. Additional doses of 0.03 g/kg were administered at intervals of 1 hr or when required to maintain anesthesia, except when no anesthetic agents were administrated for 30 mins before induction CA. The trachea was orally intubated with a 14-gauge cannula for mechanical ventilation by a volume-controlled ventilator (ALC-V9, Alcott Biotech CO., Shanghai, China) at tidal volume of 6 mL/kg. A polyethylene tubing PE50 (Instech Laboratories Inc. Plymouth Meeting, PA, USA) was advanced from the left femoral artery into the thoracic/descending aorta for measurement of arterial pressure. Through the right external jugular vein, another PE50 catheter was advanced into the right atrium for measurement of right atrial pressure and for the administration of chloral hydrate. Aortic and right atrial pressures were measured with two high-sensitivity transducers via a multiparameter patient monitor (Datascope 3000, Datascope Corp. Paramus, NJ, USA). A thermocouple microprobe (IT-21, Physitemp Instruments, Clifton, NJ, USA) was inserted into the right femoral artery and advanced to the descending aorta for measurement of blood temperature. A 5F pacing electrode with two 1 mm ring electrodes and an interelectrode distance of 5 mm was inserted orally into the esophagus of the rats about 7 cm in depth for inducing ventricular fibrillation (VF). All of the catheters were flushed intermittently with saline containing 5 IU/mL of crystalline bovine heparin.

2.2. Experimental Procedures. After collection of baseline data, VF was induced through high frequency transesophageal cardiac pacing with an alternating voltage of 24 V as previously described [30]. The stimulation was continued for 1 min to prevent spontaneous cardiac reversion. Mechanical ventilation was discontinued when cardiac pacing was started. After 5 mins of untreated CA, CPR, including manual chest compression and mechanical ventilation with air, was begun. Chest compression was performed at a rate of 200 compressions per minute, with a depth of 25%–30% of the anterior posterior diameter of the animal's chest and with equal compression-relaxation duration by the same investigator. After 1 min of CPR, one dose of epinephrine (20 μg/kg) was given through the right atrial catheter. An organized cardiac rhythm with mean aortic pressure of >60 mmHg for a minimum of 5 mins was defined as successful ROSC. CPR was continued unless the animal was either successfully resuscitated or pronounced dead after a total of 15 mins CPR.

Immediately after resuscitation, animals were randomized to hypothermic or normothermic group and monitored in an intensive care setting for additional 6 hrs. For animals assigned to TH, surface cooling was induced with the aid of ice packs and an electrical fan. Once the target temperature reached 33.5°C, it was maintained over the first 2 hr of postresuscitation and then gradually returned to 37.0°C over a rewarming period of 2 hrs. For those animals subjected to normothermic control, blood temperature was maintained at 37.0 ± 0.3°C during the 6 hrs postresuscitation observational period. All catheters, including the temperature transducer and endotracheal tube, were then removed and wounds were surgically sutured. Animals were then returned to their cages and observed for 96 hrs.

The neurological functions were assessed daily during the 96 hr postresuscitation period according to neurologic deficit scores (NDS), which was developed to evaluate neurological outcome after global cerebral ischemia for rats [31]. Details of NDS scales are illustrated in Table 1. The total score ranges from 0 to 500, representing no observational neurological deficit and brain death.

2.3. Measurements. The ECG, EEG, pressure measurements, and core temperature were continuously measured and recorded through a data acquisition system supported by WinDaq hardware/software (DATAQ Instruments Inc., Akron, OH, USA) at a sample rate of 300 Hz. Four subdermal needle electrodes (right-frontal, right-parietal, left-frontal,

Table 1: Neurological deficit score (NDS) scale.

Category	Item	Score
Level of consciousness (spontaneous attention to environment and reaction to pinching of ear or tail)	Good attention and brisk response	0
	Sluggish response and no attention	50
	No response	100
Respiration (breathing frequency)	Normal or higher (over 80/min)	0
	Decreased	50
	Apnea	100
Cornea reflex (touch center of cornea with hemostat)	Brisk	0
	Sluggish	20
	Absent	40
Cranial reflex or gag reflex (stimulation with catheter)	Brisk	0
	Sluggish	15
	Absent	30
Auditory reflex (bang metal cop with clamp)	Brisk	0
	Sluggish	15
	Absent	30
Motor sensory function (righting reflex)	Turn spontaneously	0
	Sluggish, partly	50
	No turning attempts	100
Behavior (spontaneous or stimulated)	Moving body, forward movements walking	0
	Movements of the head, looking around	50
	No movements except breathing or not at all	100

and left-parietal) placed over the surface of the skull were used for bipolar EEG measurement and recording. A two-channel EEG differential preamplifier (PRE-ISO.EEG100, Xiangyun Computing Technology, Beijing, China) was used for signal amplification and condition. The amplifier gain of each channel was set at 10,000 and the cutoff frequencies were set at 0.3 and 70 Hz for the high-pass and low-pass filters, respectively.

EEG analysis was performed offline after the experiment was concluded. All of the EEG patterns were visually annotated by an investigator and were further confirmed by another medical doctor who was blinded to the outcome. During the 6 hrs observational period, the EEG pattern was classified as one of the three following categories [25, 32]: isoelectric/suppression, burst suppression, and continuous background EEG activity. Isoelectric/suppression was defined as total absence of any visible EEG activity during a 60 secs recording episode. Burst suppression was defined by the presence of clear increases in amplitude (bursting) followed by interburst intervals of at least 0.5 sec without EEG activity or low amplitude activity (less than 10 μV). Bursts were required to have EEG amplitude >10 μV in both left and right channels. Characteristics of earlier postresuscitation EEG, including the onset time of identifiable EEG burst, the frequency of bursts during the burst suppression period, the time of recovery of continuous background EEG activity, and the spectral entropy (SE) of continuous background EEG [33], were quantitatively analyzed.

SE was calculated using the Welch averaged periodogram method from consecutive nonoverlapping epochs of 60 seconds by MATLAB 7.0 (The MathWorks, Inc., Natick, MA, USA). Linear detrending and Hanning windowing were applied to the signal before applying the Fast Fourier Transform. The sum of the magnitudes (EEG power in different subbands) in each individual predetermined frequency band that represents Delta (0.5–4 Hz), Theta (4–8 Hz), Alpha (8–13 Hz), and Beta (13–30 Hz) waves was calculated and the probability density function of each wave band was then computed as

$$p^i = \frac{X_i}{\sum_{i=1}^{N} X_i}, \tag{1}$$

where X_i represents the total energy of the ith band, p^i is the probability mass function of the spectrum in each band, and N is the total number of bands. The SE was calculated as

$$\mathrm{SE} = -\frac{\sum_{i=1}^{N} p^i * \log_2 p^i}{\log_2 N}. \tag{2}$$

2.4. Statistical Analysis. Data were presented as Mean ± SD. The 6 hrs EEG analysis and 96 hrs neurologic outcome and survival served as primary variables between experimental groups. For baseline and experimental measurements between groups, two-tailed Student's t-test was used. Quantitative EEG characteristics were analyzed by two-way analysis

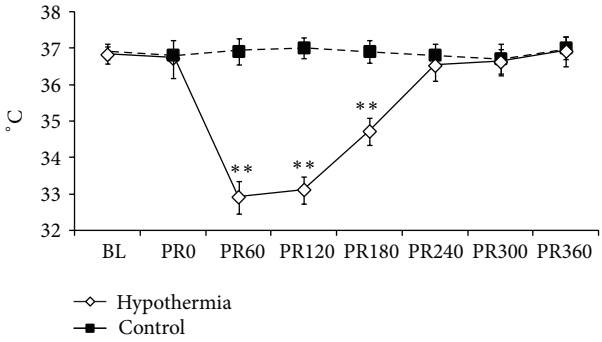

Figure 1: Core temperature before and after resuscitation. PR: post-resuscitation. $^{**}P < 0.01$ compared with normothermic control.

of variance (ANOVA) for post hoc comparison between the two experimental groups. Kaplan-Meier analysis and the log-rank test were used to calculate survival rates. The associations between characteristic indices of EEG and 96 hr neurologic outcome and survival were analyzed using Spearman's correlation and logistic regression. A $P < 0.05$ was regarded as statistically significant.

3. Results and Discussions

3.1. Results. The detailed baseline and experimental measurements are presented in Table 2. There were no differences in body weight and baseline measurements of heart rate, body temperature, and mean arterial pressure between groups.

CA was successfully induced in all animals after 1 min of transesophageal cardiac pacing. The cardiac rhythm rapidly deteriorated from VF to pulseless electrical activity (PEA) before CPR was initiated. All of the twenty rats were successfully resuscitated without the aid of defibrillatory shocks and survived to 6 hrs. No differences in the duration of CPR time (93.3 ± 19.6 versus 86.1 ± 11.9 secs, $P = 0.34$) and coronary perfusion pressure during CPR (21.6 ± 3.7 versus 21.2 ± 3.5 mmHg, $P = 0.78$) were observed between groups. Figure 1 shows the core temperature measured during the experiment. For control group, the body temperature was maintained between 36.6°C and 37.4°C during the 6 hrs observational period. For hypothermic group, the target core temperature was obtained within 26.9 mins (15.7 ± 5.0 mins) and maintained for 2 hrs.

As illustrated in Figure 2, all of the animals showed the same EEG recovery pattern during the 6 hrs EEG recording period in the order of isoelectric tracing, burst suppression, and continuous background EEG activity. However, the onset time of identifiable EEG burst (15.1 ± 1.9 versus 21.5 ± 6.0 mins, $P = 0.008$) and the time of recovery of continuous background EEG activity (171.2 ± 15.2 versus 239.5 ± 38.4 mins, $P = 0.0002$) were significantly shorter in the hypothermic group compared to the normothermic one. For rats treated with hypothermia, the frequency of burst was continuously increasing during the first 2 hrs after resuscitation. For normothermic rats, burst frequency was also increasing during the first 90 mins but this trend was not persisted at later burst suppression period. The burst frequency was significantly higher in the hypothermic group compared with that in control (Figure 3).

Since no difference in SE measurements was observed between the two EEG channels during the observational period, data were reported by the average of left and right channels. The baseline and postresuscitation SE measurements of continuous background EEG are reported in Figure 4. There were no differences in baseline measurements between groups (0.829 ± 0.133 versus 0.811 ± 0.096, $P = 0.740$). Four hrs after ROSC, the EEG evolved to continuous background activity in all of the hypothermic animals, but 5 of the normothermic animals were still on the stage of burst suppression pattern and eventually evolved to continuous background EEG activity within an additional 1 hr. Five hrs after ROSC, SE was restored to baseline in the hypothermic animals (0.741 ± 0.088 versus 0.829 ± 0.133, $P = 0.080$) and was significantly improved compared with that in normothermic ones (0.741 ± 0.088 versus 0.597 ± 0.146, $P = 0.018$), whereas a significant reduction in the control group was observed compared with baseline (0.597 ± 0.146 versus 0.811 ± 0.096, $P = 0.003$). This trend persisted to the end of the 6 hrs recording period (Figure 4) and the SE was significantly higher for hypothermic rats compared with normothermic control (0.776 ± 0.112 versus 0.563 ± 0.179, $P = 0.009$).

The neurological outcome measured by NDS was significantly better in the hypothermic animals compared with that in control during the 96 hrs postresuscitation period (Table 3). As shown in the survival curve (Figure 5), all of the hypothermic animals survived to 24 hrs and 6 of them survived to 96 hrs. On the contrary, 8 of the normothermic animals survived to 24 hrs and none survived to 72 hrs.

The correlation analysis showed that the onset time of EEG bursting ($r = 0.532$, $P = 0.016$), burst frequency at 2 hr ($r = -0.685$, $P = 0.001$), the time of recovery of continuous background EEG activity ($r = 0.692$, $P = 0.001$), and 6 hr SE ($r = -0.501$, $P = 0.024$) were correlated with 96 hr neurological outcome. Single logistic regression analysis (Figure 6) indicated that burst frequency at 2 hr postresuscitation ($P = 0.030$) and SE at 6 hr postresuscitation ($P = 0.047$) were independently predictive of 96 hr survival.

3.2. Discussion. This study demonstrated that mild hypothermia improved the recovery of earlier postresuscitation EEG by shortening the isoelectric period, increasing the burst frequency, accelerating the restoration of continuous background EEG activity, and enhancing the irregularity of brain rhythm in a rat model of CA. The results indicated that quantitative EEG characteristics of earlier postresuscitation EEG activity, including improved burst frequency during hypothermia and preserved SE during normothermia, correlated with better neurologic recovery and independently predicted 96 hr survival.

Ischemic brain injury affects synaptic transmission, axonal conduction, and cellular action potential firing in a sequential manner and plays a critical role in determining characteristics of EEG [20]. Since the EEG provides an insight into the thalamocortical function and has been used for prognostication after resuscitation from CA during normothermia, the development of accurate monitoring

Table 2: Baseline and experimental measurements.

Measurements	Hypothermia ($N = 10$)	Control ($N = 10$)	P value
Body weight, (g)	281.9 ± 34.5	295.8 ± 21.4	0.30
Heart rate, (beats/min)	389.8 ± 53.2	385.1 ± 44.0	0.83
Baseline temperature, (°C)	36.8 ± 0.2	36.9 ± 0.2	0.54
Mean arterial pressure, (mmHg)	109.9 ± 11.5	104.4 ± 16.3	0.40
Cardiopulmonary resuscitation time, (secs)	93.3 ± 19.6	86.1 ± 11.9	0.34
Coronary perfusion pressure, (mmHg)	21.6 ± 3.7	21.2 ± 3.5	0.78
Total chloride hydrate volume, (mL)	1.1 ± 0.2	0.9 ± 0.1	0.07

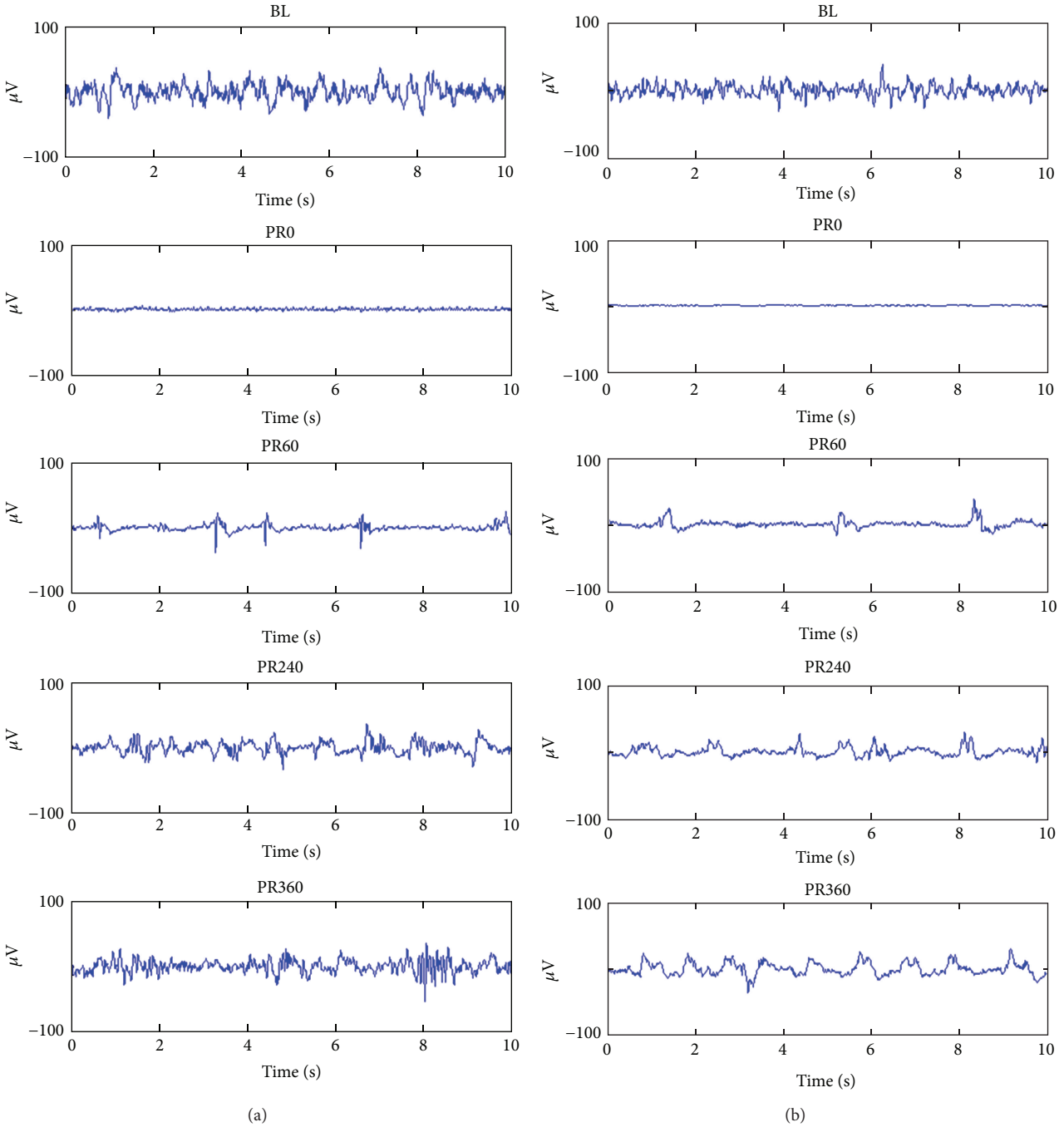

Figure 2: Examples of the evolution of EEG patterns for normothermia (a) and hypothermia (b). BL: baseline. PR: postresuscitation.

Table 3: Neurological deficit score (NDS) and survival.

Outcome	24 hr	48 hr	72 hr	96 hr
NDS				
Hypothermia	35.0 ± 9.7**	139.5 ± 199.3**	210.5 ± 249.3**	204.0 ± 254.8**
Control	370.5 ± 123.1	462.0 ± 85.0	500.0 ± 0.0	500.0 ± 0.0
Survival				
Hypothermia	10/10	8/10#	6/10#	6/10#
Control	8/10	2/10	0/10	0/10

**$P < 0.01$ hypothermic versus normothermic control with student's t-test.
#$P < 0.05$ hypothermic versus normothermic control with Fisher's exact test.

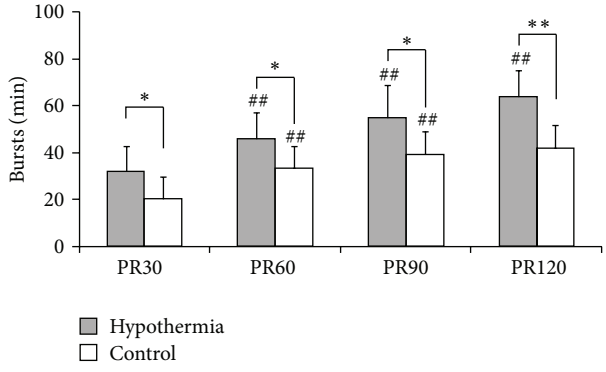

Figure 3: Burst frequency during the first 2 hr postresuscitation (PR) burst suppression period. ##$P < 0.01$ compared with previous measurement. #$P < 0.05$ compared with previous measurement. **$P < 0.01$ compared with normothermic control. *$P < 0.05$ compared with normothermic control.

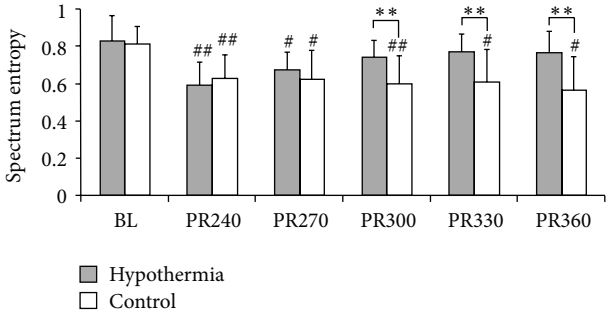

Figure 4: Spectrum entropy measurement of EEG. ##$P < 0.01$ compared with baseline. #$P < 0.05$ compared with baseline. **$P < 0.01$ compared with control. BL: baseline. PR: postresuscitation.

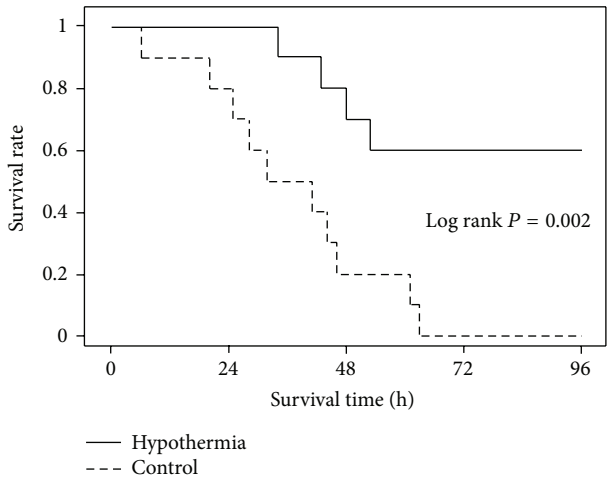

Figure 5: Kaplan-Meier analysis of cumulative survival at 96 hrs postresuscitation.

techniques employing EEG to evaluate the effectiveness of hypothermia and early prediction of neurological outcome may be anticipated [24]. Earlier studies that investigated the effects of changes in brain temperature on EEG showed that hypothermia had a similar influence on EEG in animals and humans [34]. In animal models of asphyxia, hypothermia has been demonstrated to improve EEG restoration after reperfusion by increasing the burst frequency during the early postresuscitation period [35–37]. But in another study investigating the early EEG recovery with temperature manipulation after CA in rats, Jia et al. [38] reported that burst frequency correlated strongly with 72 hr NDS in normothermic rats but not in hypothermic or hyperthermic rats. In attempt to determine a prognostic indicator, quantitative EEG analysis including cepstral distance, EEG entropy, and information quantity has been applied in animal studies [37–39]. Although these measurements were proved to be associated with neurological recovery, the prognostication for survival has not been demonstrated in these studies. Moreover, the animal model of CA induced from asphyxia was more gradual and caused different morphologic patterns of brain damage in contrast to the sudden onset of VF, which was the predominant cause of CA in out-of-hospital adults [40, 41]. Effects of temperature manipulation on EEG and its prognostic ability have also been studied in patients treated with hypothermia, in whom standard EEG was performed after they were successfully resuscitated from CA. Rundgren et al. [25, 26] found that a continuous EEG pattern at the time of normothermia was discriminative for regaining consciousness for hypothermia-treated CA survivors. Wennervirta et al. [42] demonstrated that quantitative EEG variables, including burst suppression ratio, response entropy, state entropy, and wavelet subband entropy differed between good and poor outcome groups in hypothermia-treated patients. Rossetti et al. [16] showed that hypothermia might modify the

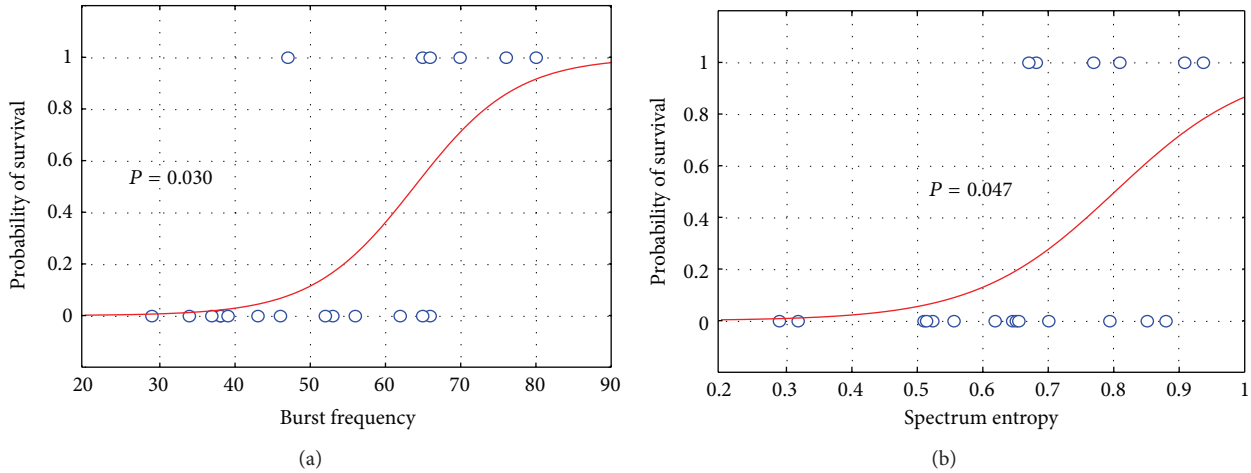

Figure 6: Logistic regression analysis of probability of survival.

outcome prediction after CA: an unreactive EEG background was incompatible with good long-term neurological recovery but strongly associated with in-hospital mortality. Leary et al. [43] reported that bispectral index (BIS) values of EEG at 24 hr postresuscitation were correlated with neurological outcomes in patients who underwent hypothermia treatment. But BIS was insufficient to predict good neurologic survival. Cloostermans et al. [27] proved that continuous EEG patterns within 12 hrs predicted good outcome while an isoelectric or low-voltage electroencephalograms after 24 hrs predicted poor outcome in patients treated with hypothermia. But the sensitivity for prediction of good outcome was low (43%). Oh et al. [44] confirmed that a continuous normal voltage EEG activity immediately after ROSC predicted good outcome, with a sensitivity of 57% and specificity of 96%. All of these studies suggested the need for continuous EEG monitoring in patients treated with hypothermia to aid in prognosis and guide management.

In our study, the recovery of EEG activity was consistent with earlier animal studies. But the isoelectric and burst suppression period were significantly shorter and the bursting frequency was significantly higher in the animals treated with hypothermia that had a good neurological outcome compared to those that were normothermic and had a poor neurological recovery. Furthermore, both the onset time of EEG bursting and the time of recovery of continuous background EEG activity were correlated with 96 hr neurological outcome. The neuroprotection effects of hypothermia therefore could be reflected by the improvements in the characteristics of early postresuscitation EEG activity, including shortening the isoelectric period, accelerating the restoration of continuous background EEG, and the increasing the frequency of burst.

Even though characteristics of burst provided important prognostic information after treated with hypothermia, but morphological pattern of EEG activity might not be entirely a marker of good/poor neurological outcome. In our study, EEG was evolved from burst suppression to continuous background activity within 5 hrs in both hypothermic and normothermic groups. This was controversial with previous reports that appearing of continuous background EEG activity was associated with good outcome [25–27, 42, 44]. To quantitatively characterize EEG waveform when continuous background activity was restored, the SE, which provides a quantitative measure of the degree of disorder in brain injury and recovery, was analyzed [45]. For animals treated with hypothermia, the SE was restored to baseline at 5 hr postresuscitation and had significantly higher values in contrast to normothermic animals. The preserved SE after the restoration of continuous background EEG activity was associated with good neurological outcome and predictive survival. C characteristics of early postresuscitation EEG activity at different stages therefore provided indicative information of hypothermic management, especially for those patients who still had a poor neurological prognostication after hypothermia therapy. The potential clinical application of this result is that severely abnormal EEG during earlier postresuscitation period with high probability of poor outcome may indicate the need for hypothermia, while EEG remains discontinuous or continuous EEG background with low probability of good outcome after rewarming may suggest a severe brain injury and the requirement for deeper/longer hypothermia or other postresuscitation cares.

There are several limitations to be considered in the current study. First, although a rat model of VF was used in this study, VF evolved to PEA after successful induction of CA in all animals and no defibrillation shock was needed to resuscitate the animals. Therefore the effect of TH on EEG activity and its prognostic value for CA that was treated with defibrillatory shocks still need to be investigated. Secondly, our study suggested that characteristics of burst suppression and preserved SE may serve as predictors of favourable neurologic outcome after CA in rats treated with hypothermia, but effects of delayed hypothermia or different cooling methods on EEG recovery have not been evaluated. Thirdly, although EEG analysis may provide useful information of neurologic recovery during TH, whether EEG measurement can be used to guide hypothermia therapy is still uncertain.

Therefore, a combination of EEG and other methods such as heart rate variability analysis together with biochemical markers may improve the prognostication capability.

4. Conclusion

The present study suggests that mild hypothermia greatly improved EEG recovery after resuscitation. Improved burst frequency and preserved SE for animals treated with hypothermia were associated with better neurological outcome and predicted 96 hr survival in this rat model of CA.

Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Bihua Chen and Feng-Qing Song contributed equally to this work.

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Research Article

Even Four Minutes of Poor Quality of CPR Compromises Outcome in a Porcine Model of Prolonged Cardiac Arrest

Heng Li,[1,2,3] Lei Zhang,[4] Zhengfei Yang,[1,2] Zitong Huang,[1,2] Bihua Chen,[5] Yongqin Li,[2,5] and Tao Yu[1,2]

[1] *Emergency Department, Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University, Guangzhou 510120, China*
[2] *Institute of Cardiopulmonary Cerebral Resuscitation, Sun Yat-Sen University, Guangzhou 510120, China*
[3] *Department of Emergency Medicine, Taiping People's Hospital, Medical School of Jinan University, Dongguan 523905, China*
[4] *Emergency Department, Southwest Hospital of the Third Military Medical University, Chongqing 400038, China*
[5] *School of Biomedical Engineering, Third Military Medical University and Chongqing University, Chongqing 400038, China*

Correspondence should be addressed to Tao Yu; dryutao@163.com

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Objective. Untrained bystanders usually delivered suboptimal chest compression to victims who suffered from cardiac arrest in out-of-hospital settings. We therefore investigated the hemodynamics and resuscitation outcome of initial suboptimal quality of chest compressions compared to the optimal ones in a porcine model of cardiac arrest. *Methods*. Fourteen Yorkshire pigs weighted 30 ± 2 kg were randomized into good and poor cardiopulmonary resuscitation (CPR) groups. Ventricular fibrillation was electrically induced and untreated for 6 mins. In good CPR group, animals received high quality manual chest compressions according to the Guidelines (25% of animal's anterior-posterior thoracic diameter) during first two minutes of CPR compared with poor (70% of the optimal depth) compressions. After that, a 120-J biphasic shock was delivered. If the animal did not acquire return of spontaneous circulation, another 2 mins of CPR and shock followed. Four minutes later, both groups received optimal CPR until total 10 mins of CPR has been finished. *Results*. All seven animals in good CPR group were resuscitated compared with only two in poor CPR group ($P < 0.05$). The delayed optimal compressions which followed 4 mins of suboptimal compressions failed to increase the lower coronary perfusion pressure of five non-survival animals in poor CPR group. *Conclusions*. In a porcine model of prolonged cardiac arrest, even four minutes of initial poor quality of CPR compromises the hemodynamics and survival outcome.

1. Introduction

Cardiac arrest (CA) is still a major public health problem around the world. It might contribute to more than 800,000 victims in western industrialized society and 540,000 in developing China annually with limited survival rate [1–3]. Over the decades, the implementation of survival chain has obtained beneficial outcomes from out-of-hospital cardiac arrest (OHCA) in some communities. Therefore, it is generally accepted and undoubtfully regarded that the measures of early chest compression and rapid defibrillation were the cornerstone of effective resuscitation especially in the absence of EMS personnel in out-of-hospital setting.

Although scene rapid defibrillation had been feasible with the aid of automatic external defibrillator (AED) and public access defibrillation (PAD), the quality of chest compression is still a critical determinant in preshock interval. Based on investigation data on animal and human, sufficient blood flow of vital organs produced by optimal cardiopulmonary resuscitation (CPR) was supposed to hold promise to the successful defibrillation following ventricular fibrillation (VF) and survival discharged with intact neurological behavior [4–6]. However, most CA patients can not usually received CPR or effective CPR whether witnessed or not. It was reported that this percentage was 37 to 42 in OHCA for those who received bystander CPR in which only 28% adhered to the target depth in the first 5 mins of CPR as guideline recommended [7, 8].

The data stated that shallow compression depth, inappropriate rate, incomplete thoracic recoil, and unnecessary

compression interruption usually lead to the failure on establishment of spontaneous circulation [1, 9–11]. All these deficiencies that exacerbated outcome were commonly seen and inevasible in actual resuscitation episode, especially for those laypersons without basic life support training. In other words, bystander CPR improves survival in CA [12], however, the quality of bystander CPR should be monitored and focused [13, 14]. In the present study, we therefore sought to evaluate the hemodynamics and resuscitation outcome in those received suboptimal quality of CPR in initial four minutes compared to good CPR originally. We hypothesized that the initial suboptimal CPR might compromise the resuscitation outcomes of cardiac arrest animals.

2. Method

2.1. Study Design. This prospective, randomized, single center and controlled experiment was designed to simulate the suboptimal bystander CPR and investigate its consequence. Experiments were performed in an established swine model of electrically induced cardiac arrest in Laboratory Animal Center of Sun Yat-sen University (Guangzhou, China). All animals received humane care and the experiments were conducted after approval of the Animal Ethics Committee, Sun Yat-sen University. The protocol was performed according to institutional guidelines.

2.2. Animal Preparation. Fourteen male Yorkshire pigs, weighting 30 ± 2 kg, were fasted overnight except for free excess to water. Anesthesia was initiated by intramuscular injection of ketamine (20 mg/kg) and completed by ear vein injection of sodium pentobarbital (30 mg/kg). Additional doses of sodium pentobarbital (8 mg/kg) were injected at intervals of approximately 1 hr to maintain anesthesia. A cuffed endotracheal tube was advanced into the trachea. Animals were mechanically ventilated with a volume-controlled ventilator (T-Bird AVIII, Bird Products Corporation, Palm Springs, CA), with a tidal volume of 15 mL/kg and FiO_2 of 21%.

For the measurement of aortic pressure, a 6F fluid-filled angiographic catheter (model 070, Cordis Corporation, Miami Lakes, FL, USA) was advanced from the surgically exposed right femoral artery into the thoracic aorta. For measurements of right atrial pressure and pulmonary arterial pressure, a 7F pentalumen thermodilution-tipped catheter (model 131HF7, Swan-Ganz TD, Edwards Life sciences, CA, USA) was advanced from the surgically exposed right femoral vein and flow directed into the pulmonary artery. For inducing VF, a 5-Fr pacing catheter (Cordis Corporation, Miami Lakes, FL, USA) was advanced from the right jugular vein into the right ventricle until an endocardial electrocardiogram confirmed endocardial contact via a multi parameter monitor (78352C, HP Corporation, Palo Alto, CA, USA). The hard gel type of adult defibrillation/pacing pads (stat-padz, Zoll Medical Corporation, Chelmsford, MA, USA) was applied with an anterior to lateral placement. An accelerometer-based handheld CPR device (CPR-D-padz, Zoll Medical Corporation, Chelmsford, MA, USA) was placed on the surface of the animal's chest just above the heart and underneath the rescuer's hands during chest compression. Cardiac output was measured by the thermodilution technique with the aid of a cardiac output computer (Baxter COM-2TM, Edwards Division, Santa Ana, CA, USA) after a bolus injection into the right atrium of 5 mL cold saline solution, which had been maintained at a temperature between 0°C and 2°C. Aortic blood gases were measured with the aid of a handheld blood analyzer (model CG4+ Cartridge, Abbott i-STAT System, Princeton, NJ, USA). Respiratory frequency was adjusted to maintain $PetCO_2$ between 35 mmHg and 40 mmHg before inducing cardiac arrest and when mechanical ventilation was resumed after resuscitation.

2.3. Experimental Procedure. After collection of baseline data, cardiac arrest was induced with a 2 mA alternating current delivered to the endocardium of the right ventricle. After VF had been successfully induced, mechanical ventilation was discontinued and cardiac arrest was untreated for a total of 6 mins. Animals were then randomized to one of the following two groups: good CPR, where manual chest compression was performed by an emergency medical doctor at a rate of 100 per min and a depth comparable to 25% of the anterior posterior diameter of the chest, which represented approximately 50 mm; poor CPR, where chest compression was operated by another emergency medical doctor at the same rate, but the chest was compressed to 70% of the depth of good CPR group, which was equivalent to approximately 17% of the anterior posterior diameter of 35 mm [8, 15]. The poor depth represented a value corresponding to the average suboptimal depth of compression recorded during out-of-hospital CPR [8, 16, 17]. During chest compression, the rescuer was blinded from the monitored compression depth and CPP values but with acknowledgment of whether his compressions were below or above 38 mm. The animal's chest wall was allowed to completely recoil in both groups. The animals were manually ventilated with a bag-valve device during CPR. Chest compression was synchronized to provide a compression/ventilation ratio of 30 : 2 with equal compression-relaxation intervals. No epinephrine or other vasopressor agents were administered. After 2 mins of compression in each group, a defibrillation was attempted with a single 120-J rectilinear biphasic shock (M-Series, Zoll Medical corporation, Chelmsford, MA, USA). Chest compression was immediately resumed followed by ECG rhythm analysis within 5 secs until confirmation of spontaneous circulation. The defibrillation attempt was regarded as successful when the electrical shock converted VF to an organized rhythm with a mean aortic pressure of ≥60 mmHg for an interval ≥10 sec [17]. If spontaneous circulation was not restored, in good CPR group, high quality chest compressions were continued for another 2 mins, after which defibrillation was attempted with another single 120 J shock, this sequence was repeated for a maximum of 5 cycles. But in poor CPR group, another 2 mins of low quality chest compressions were continued, followed another single 120 J shock, and then high quality of CPR immediately followed after defibrillation until the spontaneous circulation was restored. Otherwise,

resuscitation procedures were terminated after a maximum of another 3 high quality CPR cycles.

Catheters were removed after 1 hr of postresuscitation monitoring, and the animals were euthanized by injection of 150 mg/kg intravenous pentobarbital.

2.4. Measurement. Baseline measurements were obtained, including ECG, the aortic pressure, right atrial pressure, cardiac output, and blood gas analysis. The ECG, pressure measurements and acceleration signals were continuously measured and recorded through a data acquisition system supported by Windaq hardware/software (Dataq Instruments Inc., Akron, OH, USA) at a sample rate of 300 Hz. The coronary perfusion pressure (CPP) was digitally computed from the differences in time-coincident diastolic aortic and right atrial pressures. The compression rate and depth were calculated from the double integration of acceleration signals recorded from accelerometer by MATLAB7.0 (The Math Works, Inc., Natick, MA, USA).

2.5. Statistical Analyses. Data are presented as mean ± standard deviation (SD). Differences in compression depth and CPP between the two groups were analyzed by two-tailed Student's t-test for independent samples test. A two-tailed Fisher's exact test was performed for rate comparison. A P value <0.05 was regarded as statistically significant.

3. Results

Baseline measurements did not differ significantly between the two groups before inducing cardiac arrest (Table 1).

During initial 2 mins of CPR, the measured compression depth was ranged from 19.00 to 38.50 mm in poor CPR group and between 35.20 and 57.00 mm in good CPR group. As shown in Figure 1, the compression depth was significantly higher in good CPR group during the first 2 mins of chest compression ($P < 0.05$). As anticipated, CPP was significantly higher in good CPR group compared with poor CPR group ($P < 0.05$, Figure 2).

In poor CPR group, the measured compression depth of the first 4 mins of CPR significantly increased after is being changed to good quality compression for the last 6 mins of CPR (30.40 ± 4.70 versus 44.70 ± 6.80, $P < 0.05$). However, the CPP of the animals in this group was not significantly increased correspondingly, as shown in Figure 3.

The defibrillation success rate for the first shock was higher in the good CPR group than in the poor CPR group, but a statistical significance was not achieved (100% versus 71.43%, $P = 0.46$). In poor CPR group, although VF was terminated in 5 pigs after the first shock, 3 animals were sustained in pulseless electric activity (PEA) without ROSC after 10 mins of resuscitation efforts.

All of the 7 animals had ROSC after high quality compressions, while only 2 of the animals had ROSC with 4 mins of low quality compressions (100% versus 28.57%, $P = 0.021$). No rib fractures were observed in both groups.

Table 1: Baseline characteristics.

	G-CPR ($n = 7$)	P-CPR ($n = 7$)	P value
Body weight (kg)	31.64 ± 2.37	31.93 ± 2.42	*0.82*
Thoracic A-P diameter (cm)	22.27 ± 0.56	22.07 ± 0.73	*0.58*
Hemodynamic status			
Mean aorta pressure (mmHg)	103.86 ± 21.67	105.14 ± 14.01	*0.90*
Right atrium pressure (mmHg)	1.24 ± 0.77	0.93 ± 0.67	*0.43*
Heart rate (bpm)	112 ± 12.70	114.29 ± 13.94	*0.75*
Cardiac output (L/min)	4.76 ± 0.72	4.49 ± 1.19	*0.76*
Blood-gas analysis			
Core temperature (°C)	37.90 ± 0.42	38.10 ± 0.58	*0.47*
pH	7.49 ± 0.10	7.54 ± 0.13	*0.39*
$PaCO_2$ (mmHg)	36.61 ± 1.85	36.36 ± 1.26	*0.77*
PaO_2 (mmHg)	81.29 ± 8.54	83.00 ± 9.49	*0.73*
Lactate (mmol/L)	1.76 ± 0.30	1.86 ± 0.34	*0.57*

Based on analysis of variance test as appropriate. Values are expressed as mean ± SD.

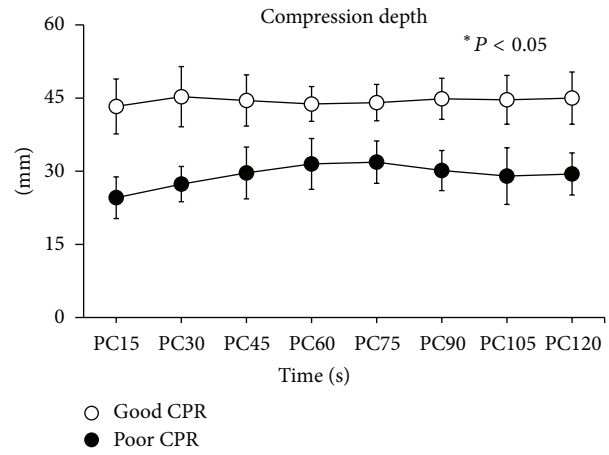

Figure 1: Comparison of compression depth values between the two groups during initial 2 mins of cardiopulmonary resuscitation. *$P < 0.05$. PC = chest compression.

4. Discussion

Our present study demonstrated that initial 4 mins of low quality compression followed by high quality of CPR compromised the outcomes significantly compared with good CPR from the beginning. Additionally, we also found that coronary flow produced by subsequent optimal chest compression could not provide a favorable outcome to those who experienced a low quality of CPR.

Base on previous studies and the current guideline, early and immediate bystander CPR was of importance in treating arrest patients before paramedic arrived, and if it is available, it may improve outcome on survival and neurological

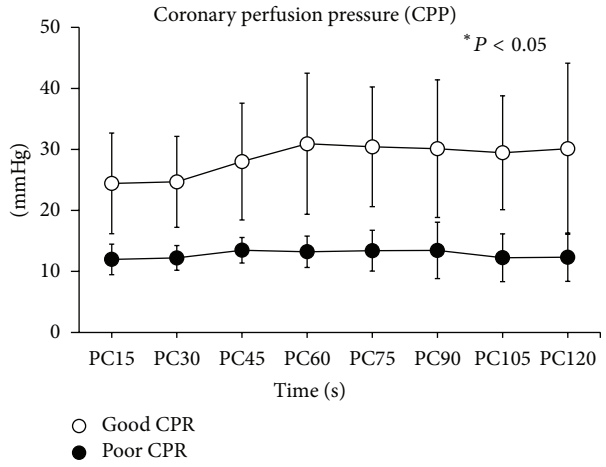

Figure 2: Comparison of coronary perfusion pressure (CPP) values between the two groups during initial 2 mins of cardiopulmonary resuscitation. $^{*}P < 0.05$. PC = chest compression.

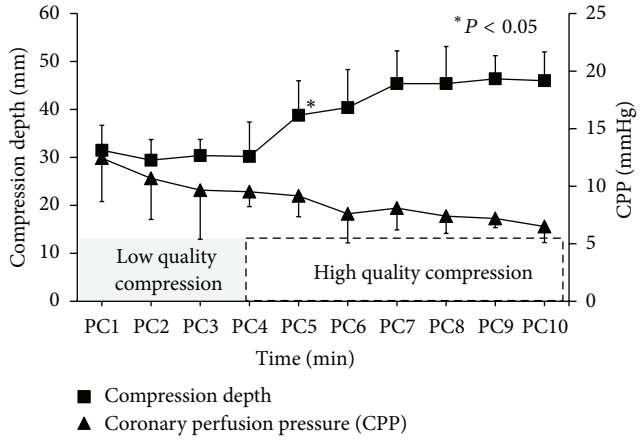

Figure 3: The characteristics of compression depth and coronary perfusion pressure (CPP) in poor CPR group during the entire 10 mins of cardiopulmonary resuscitation procedure. PC = chest compression.

function. However, initiation of CPR for a bystander was still hesitating and the quality of this CPR was rarely satisfying. In a perspective observational trial by Kitamura and his team [7], they pointed out there were only 40% laypersons that which tended to perform CPR when witnessed a collapse patient. In the scenarios of cardiac arrest, only 24% of chest compressions performed by untrained laypersons reached the target depth of 38 to 51 mm. The situation still did not take a favorable turn when bystander was a professional physician. Studies carried out by Wik and his colleagues [8] had demonstrated that only 30% of compression depth reached a target value of 31–50 mm in the first 5 mins of CPR and even undertook by ambulance personnel, and nearly half of those compressions (47%) did not achieve the adequate depth even under the condition of application of automated feedback system to assist CPR. Incomplete compression was usually performed in prehospital setting either by layperson or physician.

For chest compression, the fact that CPP was a positive associated with compression depth had been well documented. Sufficient compression depth may bring better blood perfusion to cardiomyodium and produce optimistic resuscitation outcome in animal model of prolonged VF and CPP of ≥15 mmHg in the period of chest compression was considered as an essential condition with the purpose of subsequently successful electrical shock and return of spontaneous circulation [18]. In our present study, it maintained a level of 12 to 15 mmHg in poor CPR comparing with 25 to 30 mmHg in good CPR during the first 2 minutes of chest compression. Similarly, Babbs et al. firstly demonstrated a linear relationship displayed between depth and cardiac output in the range of 23 to 60 mm in the canine model of VF [19]. Besides, according to analyzing the electrocardiogram waveform of VF during compression, Li and his colleagues also concluded that CPP had improved accompanying with the increasing depth [17]. However, in our present study, when compression was transformed from suboptimal to optimal pattern, CPP still persistently declined even a 6 mins of optimal compression was provided. One of the possible explanations this decreasing CPP may be presented with an elevated right atrial pressure contributed to a "stone heart" observed in final autopsy and described by Ventura-Clapier as global ischemic contracture resulting in firm myocardium [20]. It was a deleterious network that decreased coronary blood flow exacerbating ischemia-induced myocardial stiffness when spontaneously coupled with the gradual rising right atrial pressure further precluded coronary perfusion.

The other explanation of deteriorative CPP in following optimal compression might be partially contributed to the decreasing compliance of chest. After 4 mins of low quality of compression, the thoracic elasticity decreased. Then incomplete recoil of chest wall and subsequently decreased CPP and myocardial blood flow even only 10–20% leaning attended in CPR.

Rapid defibrillation has been recommended as a critical and primary treatment for cardiac arrest with initial shockable rhythm as VF or pulseless ventricular tachycardia (VT) [21]. To produce higher success of defibrillation, outcome was primarily determined by two factors: shock time and blood flow of myocardium. In our present study, shock was attempted every 2 mins when ECG was still VF or VT. It was also coincident with the current guideline as 5 cycles of CPR (approximately 2 mins) following by a single 120-J shock. The blood perfusion of heart was essentially associated with performance of CPR. Delayed shocks usually indicated prolonged ischemia and poor CPR brought insufficient perfusion to stiff myocardium. In an observational study of adult cardiac resuscitation [22], the investigator demonstrated that successful defibrillation was associated with shorter preshock pause and higher mean compression depth. Similar results came from a laboratory investigation, the investigator concluded that coronary flow had a strong positive relationship with CPP and the final resuscitation depended on this "threshold CPP" [23]. This might be the answer that two animals in poor CPR group achieved ROSC

in first shock with average CPP of 13.50 to 13.80 mmHg, which was close to 15 mmHg.

The finding of this study indicated that there was no statistic difference of the first shock success in both groups. However, 5 animals in poor CPR group failed to return perfused rhythm and functional arterial pressure which finally lead to the significant difference with subsequent final ROSC. For a cardiac arrest porcine model, 6 mins of untreated VF was not long enough to guarantee the difference. A canine model of 5 mins of VF demonstrated that immediate defibrillation without preshock CPR brought none of animals ROSC (0/10), but resulted in 30% successful defibrillation (3/10) [24]. In a prospective cohort study, Stiell found that there was only of 25.7% patients who returned spontaneous circulation with 36.6% of bystander CPR and 46% of EMS compression depth within recommended range. As previously reported, they also did not notify the outcome in those bystander and subsequent EMS CPR group but declared a strong association between survival outcomes and increased compression depth [25]. In a porcine model of 4 mins of VF, Wu compared two different patterns of chest compression and found that the standard compression (rate: 100 ± 5 cpm, depth: 50 ± 1 mm) produced higher ROSC and survival rate than that in simulated clinical compression (rate: 80 ± 5 cpm; depth: 37 ± 1 mm) [26]. Besides, they acquired similar results as ours in shock attempts without consideration of resuscitation procedure. These conclusions may be partially supported by the concept of "circulatory phase," a time-duration definition that ranges from approximately 4 to 10 mins of VF [27]. Outcomes were prone to be improved when some limited blood circulation with partial substrates was established prior to defibrillation. In our present study, it was the 2 mins of optimal CPR rather than 4 mins of suboptimal CPR, which could make the different ischemic myocardial condition to prepare for the coming counter shock.

It is well known that, with every minute without CPR following sudden cardiac arrest, the probability of survival reduces by 7%–10% per minute [28]. When bystander CPR is delivered, the patient stands a better chance as the probability for survival reduces to 3%-4% per minute. Overall, bystander CPR increases that survival 2-3 times compared to no bystander CPR [13, 14, 29]. When Health Care Professionals deliver quality CPR, research indicates survival rates can increase 4 times, compared to poor CPR [30–32]. Our present study also demonstrated the importance of CPR quality in the initial 4 mins during CPR. In most regions and countries, it can be speculated that no less than 4 mins would be taken to activate and receive EMS assist without satisfying communication and traffic condition [33]. Instead of health care professionals, bystander CPR was encouraged to deliver these basic life support as soon as witnessed an arrest presumed a cardiac origin. The initial quality of compression should be guaranteed by the rescuer, so good training system and useful tools for CPR quality monitor and guidance were totally welcome for the future implementation [34].

We realized that there were some limitations in this study. Firstly, we did not compare the poor CPR group with prolonged (10 mins) untreated VF animals to evaluate if the initial poor rescue action might result in worse outcomes. We need deeply investigation to answer this question. Secondly, the healthy swine model is not always indicated a real condition of patients in clinical setting. People in VF usually suffered from coronary artery occlusion or asphyxia; besides, the successful resuscitation are not usually benefited from only CPR and counter shock if suspected coronary artery was not under revascularization. After all, despite these limitations existed, the facts that the suboptimal CPR impaired CPP was confirmed, and if it occurs, even a delayed optimal CPR may fail to improve the limited survival opportunities.

5. Conclusion

In this porcine model of prolonged cardiac arrest, even four minutes of initial poor quality of CPR compromises the survival outcome.

Conflict of Interest

The authors declare no conflict of interests.

Acknowledgments

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