Dynamic Course of Clinical State Transitions in Patients Undergoing Advanced Life Support after Out-of-Hospital Cardiac Arrest

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ABSTRACT

Objectives: Studies of out-of-hospital cardiac arrest generally document the presenting (pulseless electrical activity [PEA], ventricular fibrillation/tachycardia (VF/VT), asystole), and the final states (resuming stable spontaneous circulation [s-ROSC], being declared dead). Only a few studies described the transitions between clinical states during advanced life support (ALS). The aim of this study was to describe and analyze the dynamics of state transitions during ALS.

Methods: A retrospective analysis of 464 OHCA events was conducted. Any observed state and its corresponding changing time were documented through continuous electrocardiographic and trans-thoracic impedance recording.

Results: When achieved, most s-ROSCs were obtained by 30 min, regardless of the presenting state. After this time point, the persistence of any transient state was associated with a great probability of being declared dead. The most probable change for VF/VT or PEA at any time was the transition to asystole (36.4% and 34.4%, respectively); patients in asystole at any time had a 70% probability of death. Patients achieving s-ROSC mostly came from a VF/VT state.

In most cases, the presenting rhythm tended to persist over time during ALS. Asystole was the most stable state; a higher degree of instability was observed when the presenting rhythms were VF/VT or PEA. Transient ROSC episodes occurred mainly as the first transition after the presenting state, especially for initial PEA.

Conclusions: An understanding of the dynamic course of clinical state transitions during ALS may allow treatment strategies to be tailored in patients affected by OHCA.

Introduction

In patients suffering from out-of-hospital cardiac arrest (OHCA), the presenting rhythm—namely pulseless electrical activity (PEA), pulseless ventricular tachycardia (VT), ventricular fibrillation (VF), or asystole—has been described as an independent predictor of survival (1) and specific algorithms were recommended to treat patients presenting with VF/VT, PEA, and asystole. However, during advanced life support (ALS) the presenting rhythm is expected to change to a different clinical state over time. Indeed, the international guidelines for cardiopulmonary resuscitation (CPR) recommend, while ensuring high quality CPR, adapting the resuscitative interventions at each change of the above states; for example, by providing defibrillation, administering tailored medications, or identifying and treating the underlying cause of OHCA, as appropriate (2). As a result, before achieving a final stable state (i.e., resuming a spontaneous circulation [ROSC] or being declared dead) the presenting clinical state may remain unchanged, or may change one or more times to a different transient state (i.e., VF/VT, PEA, or asystole). In addition, ROSC could sometimes be achieved transiently, with a subsequent return to a no-circulation state.

Unfortunately, most studies of cardiac arrest are limited to documenting the presenting rhythm and the final state, while only a few studies have described in detail the transitions between clinical states during ALS (3–5). Moreover, little is known about whether a maximum time threshold is identifiable by which a patient undergoing ALS is expected to achieve a stable ROSC state. In addition, although the occurrence of transient ROSC has been described as a favorable prognostic factor (5–7), little is known about the timing of a transitory ROSC occurrence and toward which state it tends to evolve. A greater knowledge of the characteristics, frequency, and probability of state transitions might allow tailored treatment strategies to be considered, which are currently not clearly definable (8, 9).

The main aim of our present study was to describe and analyze the dynamics of state transitions during ALS, according to the presenting rhythm and the final state, and to identify a possible time interval beyond which the probability of achieving a stable ROSC state is drastically reduced. Moreover, we analyzed in detail the OHCA

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episodes presenting transient ROSC states, aiming to identify possible patterns of interest in state transitions.

Methods

Study Design, Setting and Population

This was a retrospective analysis of prospectively collected real-time data carried out in the emergency medical service (EMS) of Trieste (Italy).

CPR was more frequently started by basic life support (BLS) teams due to their greater and more widespread presence. ALS teams were dispatched contemporary to BLS ambulances. ALS teams included experienced emergency physicians able to administer intravenous medications and provide advanced airway management by tracheal intubation or, alternatively, by supraglottic devices. ALS teams were equipped with LIFEPAK defibrillators (LP-12 or LP-15, Physio-Control, Redmond, WA, USA), which allowed continuous ECG and trans-thoracic impedance (TTI) recording, while these devices were not available for BLS ambulances. Consequently, only patients cared for by ALS teams were considered for inclusion in the study.

Patients' data collection was approved by the Regional Ethical Committee (nr. 09/2016/os). All consecutive adult patients undergoing ALS from January 1, 2016 to December 31, 2019 with complete data recording were included. Advanced life support events presenting as asystole and lasting less than five minutes with patients declared dead were excluded, assuming on-scene determination of futility.

Data collection and Processing

Upon arrival at the OHCA site, ALS teams started or continued CPR (in cases where it was already started by BLS teams or bystanders). Defibrillator pads were promptly connected to check ECG rhythm, simultaneously activating real-time ECG and TTI recording. Defibrillation was provided whenever a state of VF/VT occurred, and CPR resumed as appropriate. The decision to discontinue ALS was made by the emergency physicians based on specific conditions such as the patient's relevant comorbidities or total length of CPR (also including possible CPR performed before arrival at ALS). No patient was transported to the hospital with ongoing CPR. After ending ALS, the defibrillator-recorded events—anonymized through an automatically generated code—were transferred by modem to a central server.

Each OHCA event was analyzed using the Code-Stat™ software (release 9.0, Physio-Control Inc., Redmond, WA), which displayed ECG and TTI traces on continuous graphs reflecting the actual time of the events. Any observed state and its corresponding changing time in each ALS event, from defibrillator connection (i.e., soon after the ALS team arrived) until the termination of resuscitative efforts, was documented. A deflection of variable amplitude in the TTI trace documented impedance changes related to lungs' inflation, left ventricular systole, and chest compressions (10–12). Accordingly, when considered together with the ECG trace, changes in TTI signal allowed distinguishing of pulse-generating rhythms from PEA (13–15), according to the method described elsewhere (6, 16). In brief, all stages of CPR in which CodeStat displayed an interruption of chest compressions in the presence of an organized ECG activity were identified and analyzed to differentiate PEA from pulse-generating rhythms. PEA was defined as QRS-complexes >40 beats/min without any associated change in TTI induced by blood flow. When QRS-associated modifications ("bumps") in TTI signal were found, the condition was identified as a ROSC state and classified as follows, according to previous literature:

- "transitory" (t-ROSC), when the state lasted more than one minute with a subsequent resumption of chest compressions (3, 5);
- "sustained" (s-ROSC), if the state persisted until the patient arrived at the hospital emergency department (17).

The VT, VF, and asystole states were recognized according to Utstein's recommendations (18). For the study's purposes, VF and VT were considered as a single VF/VT state. Asystole, VF/VT, PEA, and t-ROSC were considered as "transient" states, whilst s-ROSC and "dead on scene" (DOS) were defined as "final" states. The first monitored rhythm at defibrillator connection (i.e., asystole, VF/VT, or PEA) was labeled as the "presenting" state.

In general, changes in states were documented during hands-off times (i.e., absence of chest compressions recognized in the analysis) to avoid misinterpretation related to biases in ECG or TTI signals due to the simultaneous chest compressions. However, in cases of a rhythm clearly detectable during chest compressions, the state was documented at the first visible change, pending its confirmation at the subsequent compression pause.

Analysis

Normality of the data distribution was assessed by the Kolmogorov-Smirnov test. Continuous variables were displayed as median and interquartile ranges (IQR), and nominal variables as number and percentage. Unadjusted comparisons between the groups were analyzed *via* a χ^2 test, a non-parametric Mann-Whitney's U test for independent samples, or a Kruskal-Wallis test adjusted by the Bonferroni correction for multiple pairwise comparisons, as appropriate.

The modification of clinical states was described through plots displaying the proportion of subjects who were in a certain state over ALS time, with a one-minute resolution. Patients were also stratified according to the final state (i.e., patients who achieved s-ROSC or who were declared DOS) and the presenting clinical state. Moreover, based on time thresholds identified by actual ALS duration in the study population, separate analyses of state transitions were performed according to the state detected at an early (after 10 min, T_{10}), intermediate (after 20 min T_{20}), and late (after 30 min, T_{30}) time.

Statistical analysis was performed using IBM software SPSS Statistics, release 24.0 (Armonk, NY, US). For all tests, an alpha level of $p < 0.05$ was set for statistical significance.

Results

During the study period, 495 patients underwent ALS with simultaneous TTI and ECG recording. Among them, 31 were excluded because they presented asystole CPR lasting less than five minutes without any ROSC. Thus, 464 OHCA patients constituted the final study population. Table 1 shows the main characteristics of the subjects included in the research.

Transition of Clinical States Over-Time

Overall, the median number of state transitions (all states) per ALS episode was two (IQR 2–4; range 2–10). Figure 1 shows the clinical states' prevalence over-time, overall, and according to the presenting clinical state; the modification of state prevalence at T_{10}, T_{20}, and T_{30} is presented as well. The transient state with the higher prevalence was that recognized as the presenting state (Figure 1(b–d)).

At T_{10} and T_{20} time points, 79% and 44% of subjects were still in a transient state (VF/VT, PEA, asystole, or t-ROSC), respectively (Figure 1(a)). After grouping patients based on the presenting state, no difference between patients who were still in a transient state was found at T_{10} ($p = 0.070$) and T_{20} ($p = 0.549$) (Table 2). Conversely, at T_{30} a larger proportion of subjects ($p = 0.010$) achieved a final state in the asystole sub-group (Table 2).

Starting from T_{30} (i.e., 30 min after beginning ALS) a clear curve flattening was observed for patients who achieved s-ROSC (Figure 1(a)). This finding was similar for patients presenting in asystole, PEA, or VF/VT states, although the respective prevalence of the s-ROSC state at T_{30} was largely different (VF/VT: $n = 36$, 43.4%; PEA: $n = 23$, 17.3%; asystole: $n = 18$, 7.3%; $p < 0.001$) (Figure 1(b–d)).

Table 1. Main characteristics of the study population.

Age (years)	78; 64–86
Sex (males)	290 (62.5%)
Etiology of cardiac arrest	
Presumed cardiac	333 (71.8%)
Other noncardiac	15 (3.2%)
Not established	116 (25.0%)
Ongoing CPR at ALS arrival	438 (94.4%)
First documented clinical state	
Asystole	248 (53.4%)
PEA	133 (28.7%)
VF/VT	83 (17.9%)
Interval emergency call to ALS (min)	10 (3–15)
ALS on-scene time (min)	19 (12–27)
On scene sustained ROSC	
All presenting clinical states	81 (17.5%)
Presenting with asystole	19 (7.7%)
Presenting with PEA	25 (18.8%)
Presenting with VF/VT	37 (44.6%)

CPR: cardiopulmonary resuscitation; PEA: pulseless electrical activity; VF/VT: ventricular fibrillation/tachycardia. ROSC: return of spontaneous circulation. ALS: advanced life support. Data are presented as "number (percentage)" or "median; interquartile range".

Patients presenting one or more state transitions ($n = 45$; 21.8%) had a statistically significant higher rate ($p = 0.026$) of s-ROSC when compared to those who reached the final state without modifying their presenting state ($n = 36$; 14.0%). Patients with asystole as a presenting state showed a higher likelihood to reach a s-ROSC or being declared DOS without any state transition (asystole: $n = 181$, 73.0%; PEA: $n = 53$, 39.8%; VF/VT: $n = 24$, 28.9%; $p < 0.001$).

Figure 2 shows state transitions separately for patients finally achieving an s-ROSC or declared DOS. In patients who achieved s-ROSC, the proportion of patients who were still in transient state (VF/VT, PEA, asystole, or t-ROSC) was similar at the three considered time points. Conversely, in patients who were ultimately declared DOS rhythm transitions continued longer, and this condition was significantly different among VF/VT, PEA, and asystole sub-groups throughout the ALS time (Table 2).

State Transition Probability

A state transition analysis, representing the overall probability of achieving a certain state after being in a transient state at any time during ALS, is demonstrated in Figure 3. The most probable state transition for a patient VF/VT state at any time was transition to asystole (36.4%) followed by PEA (24.0%), whilst when in PEA at any time the higher probability was a transition to asystole (34.4%) or being declared DOS (32.8%). Patients in an asystole state had a lower probability of change toward another transient state, having almost 70% probability of being declared DOS. The most frequently documented transition after a t-ROSC was PEA. Patients who achieved s-ROSC mostly came from a VF/VT state.

Prevalence of Transitory ROSC State

Thirty-three patients (7.1%) presented one or more t-ROSC states. In the whole population, the occurrence of t-ROSC states was associated with a higher probability of achieving s-ROSC (with t-ROSCs: $n = 14$, 42.4%; without t-ROSCs: $n = 67$, 15.5%; $p < 0.001$). After considering the sub-group of state presentation, the association was confirmed only in patients having asystole as a presenting rhythm (with t-ROSCs: $n = 5$, 50%; without t-ROSCs: $n = 14$, 5.9%; $p < 0.001$).

Figure 4 shows the details of 33 patients manifesting t-ROSCs. In 70% of cases ($n = 23$), t-ROSC was the status immediately following the presenting state. Overall, t-ROSCs lasted for a median of 2:14 min (IQR 1:21–3:39) and presented a single time in most patients ($n = 27$; 81.8%).

In all patients presenting with VF/VT who achieved s-ROSC, t-ROSC presented in the first 13 min of ALS, while all patients with t-ROSC presented later were declared DOS. A similar pattern was observed in patients presenting in asystole, while the association between the timing of t-ROSC and s-ROSC seemed more unpredictable in cases of PEA.

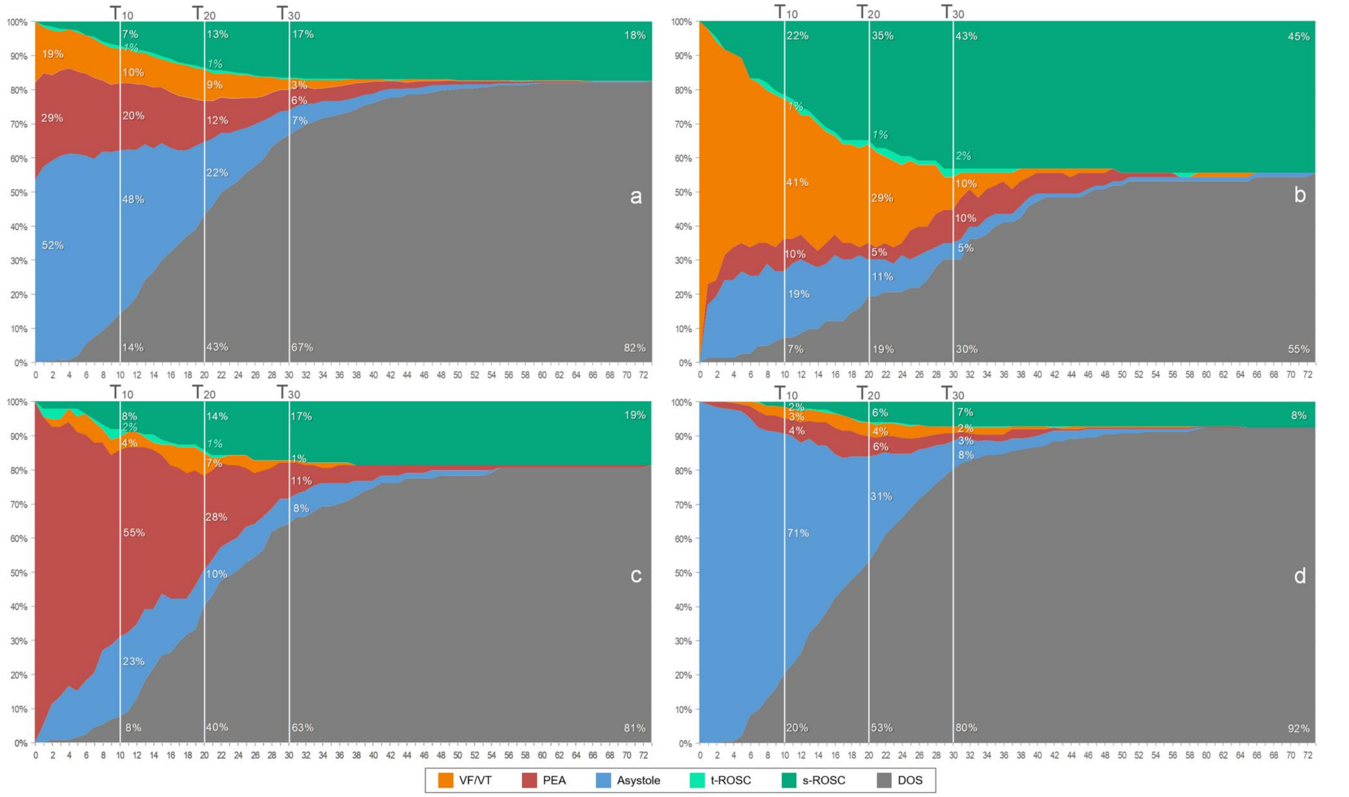

Figure 1. Modification of clinical states prevalence over-time: (a) in the whole study population; (b) in patients having VF/VT as a presenting state ($n = 83$); (c) in patients having PEA as a presenting state ($n = 133$); (d) in patients having asystole as a presenting state ($n = 248$). Continuous white lines (T_{10}, T_{20}, T_{30}): time thresholds of ALS duration. PEA: pulseless electrical activity; VF/VT: ventricular fibrillation/tachycardia. ROSC: return of spontaneous circulation. t-ROSC: transient ROSC. s-ROSC: stable ROSC. ALS: advanced life support. DOS: dead on scene.

Table 2. Dynamic evolution of transient clinical states according to the presenting rhythm and the final states.

Presenting rhythm	Still in transient state at:	All episodes	*p*-Value	Group s-ROSC	*p*-Value	Group DOS	*p*-Value
VF/VT		59 (71.1%)		19/37 (51.4%)		40/46 (87.0%)	
PEA	T_{10} (10 min)	112 (84.2%)	0.070	14/25 (56.0%)	0.128	98/108 (90.7%)	0.012
Asystole		194 (78.2%)		15/19 (78.9%)		179/229 (78.2%)	
VF/VT		38 (45.8%)		8 (21.6%)		30 (65.2%)	
PEA	T_{20} (20 min)	61 (45.9%)	0.594	6 (18.8%)	0.966	55 (50.9%)	0.016
Asystole		102 (41.1%)		4 (21.1%)		98 (42.8%)	
VF/VT		22 (26.5%)		1 (2.7%)		21 (45.7%)	
PEA	T_{30} (30 min)	25 (18.8%)	0.010	2 (8.0%)	0.638	23 (21.3%)	<0.001
Asystole		31 (12.5%)		1 (5.3%)		30 (13.1%)	

Proportion of patients having had VF/VT, PEA or asystole as a presenting rhythm and who were still in a transient state (VF/VT, PEA, asystole or t-ROSC) at the study time-points, overall (see Figure 1(b–d)) and in subgroups of those who finally achieved a s-ROSC (see Figure 4(c,e,g)) and who were finally declared DOS (see Figure 4(d,f,h)). Data presented as a number (percentage).

Discussion

In a population of OHCA patients, the probability of achieving s-ROSC decreased dramatically after 30 min of ALS (Figures 1 and 2) regardless of the presenting state, despite ALS often continuing for a longer time. After this time point, the persistence of any transient state was associated with a great likelihood of being declared DOS. Our results are different from those of a previous study that focused on OHCA, reporting that a steady and definitive prevalence of s-ROSC was reached more rapidly in cases of asystole (15 min) and PEA (20 min) than VF/VT (30 min) (5). Conversely, our findings are in line with a previous study focused on in-hospital cardiac arrest (IHCA), showing that the large majority of patients who obtained s-ROSC reached this state by 20 min of ALS, irrespective of the presenting rhythm, while the persistence of instability in state dynamics beyond this time point led to a high risk of death (3).

The fact that resuscitative interventions may have been less effective in achieving s-ROSC after a certain time interval should not be surprising. Indeed, patients undergoing prolonged resuscitation are exposed to a number of major pathophysiological complications, also worsening the myocardial function, which are critically time dependent (19). In general, a shorter duration of CPR is associated with a better neurological outcome in OHCA survivors, although it is possible to survive with a good neurologic outcome after a prolonged resuscitation (20, 21). The CPR time is only one of the factors affecting the prognosis after OHCA, which may be related to conditions such as CPR promptly started by bystanders, earliness of defibrillation, etc. On this basis, the actual termination strategy suggests

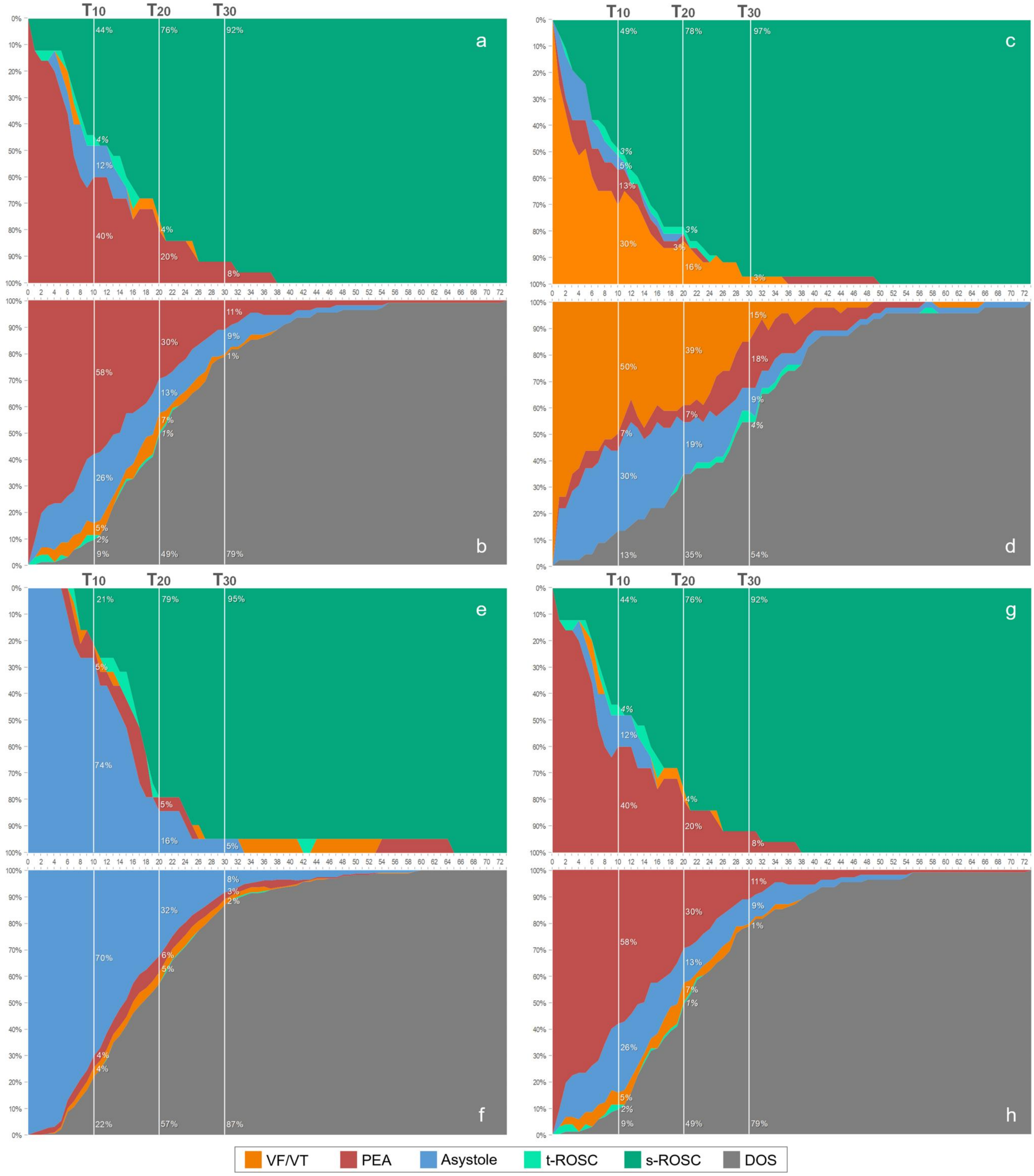

Figure 2. Modification of clinical states' prevalence over-time for patients finally achieving an s-ROSC or declared DOS: (a) in the whole study population; (b) in patients having VF/VT as a presenting state ($n = 83$); (c) in patients having PEA as a presenting state ($n = 133$); (d) in patients having asystole as a presenting state ($n = 248$). Continuous white lines (T_{10}, T_{20}, T_{30}): time thresholds of ALS duration. PEA: pulseless electrical activity; VF/VT: ventricular fibrillation/tachycardia. ROSC: return of spontaneous circulation. t-ROSC: transient ROSC. s-ROSC: stable ROSC. ALS: advanced life support. DOS: dead on scene.

that ALS may be ceased when asystole persists for more than 20 min in the absence of identified reversible causes, but only as long as the cardiac arrest was unwitnessed, bystanders did not commence CPR, no defibrillation was delivered, and no t-ROSC occurred (22). Consequently, a precise time threshold beyond which the probability of an unfavorable outcome becomes dramatically prevalent is very difficult to determine (23).

In the present investigation, we found that the transient state with the higher prevalence was that recognized as the presenting state in VF/VT, PEA, and asystole sub-groups. This finding is in line with previous research, demonstrating that

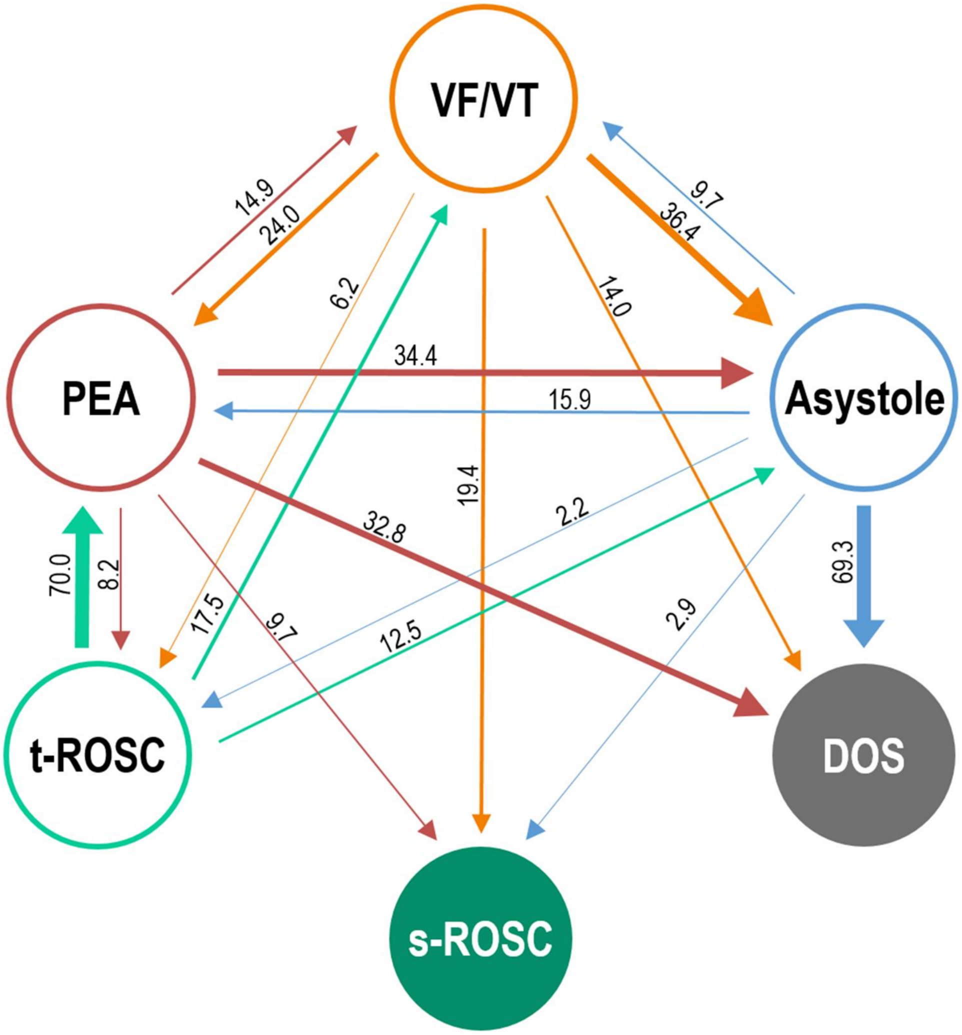

Figure 3. State transition diagram, representing the overall probability of achieving a certain state after being in a transient state at any time during ALS for a patient suffering from OHCA. The arrows represent the direction of state transition, the numbers next to the arrows and their thickness the probability (%) of transit to the subsequent state. PEA: pulseless electrical activity; VF/VT: ventricular fibrillation/tachycardia. ROSC: return of spontaneous circulation. t-ROSC: transient ROSC. s-ROSC: stable ROSC. ALS: advanced life support. DOS: dead on scene.

the initial state tends to be maintained: the higher the proportion of time spent by a patient in a certain transient state, the higher the chance that they returned to or remained in that state (9). Asystole was found to be the most stable state, while a higher degree of state instability was observed when the presenting rhythm was VF/VT or PEA. Indeed, three out of four patients having asystole as their presenting state did not show any transient state before achieving s-ROSC or being declared DOS, while more than half of those in VF/VT or PEA experienced one or more state changes before achieving a final clinical state. While for VF/VT this finding was expected—as its treatment involves defibrillation after which a change of state is predictable, it was more surprising with respect to PEA. Pulseless electrical activity was previously described as a state more unstable than asystole in IHCA (24), but not in OHCA patients (5). PEA represents a complex condition, often secondary to acute myocardial ischemia, heart failure, or coronary artery disease (25), which can be associated with very different organized cardiac electrical activity of either sinus, supraventricular, or ventricular origin, having markedly different QRS rate, morphology, width, and amplitude. The ECG characteristics associated with PEA have been found to be associated with patient outcome (26, 27). Despite an impalpable pulse, the organized cardiac electrical activity can be associated either with the presence of cardiac mechanical activity (pseudo-PEA) or not (true PEA). Pseudo-PEA can be the expression of very unstable hemodynamic states (28, 29). Similar to VF/VT, state transitions in PEA may be related to electric and pharmacologic treatment (30). For all the above reasons, both VF/VT and PEA should be considered as states having a high propensity to change over-time. These dynamics may be related to the etiology of cardiac arrest, concurrent patient acute or comorbid conditions, as well as the different time of adrenaline administration according to the presenting rhythm (3, 31). However, this finding should be interpreted with caution, since many conditions not considered by the present study (e.g., the effective presenting rhythm at OHCA onset before starting ALS, bystander CPR and defibrillation, patient comorbidities, etc.) may have affected both the number of state transitions and the short-term outcome.

In the present study, we performed a separate analysis of episodes presenting t-ROSC states. We observed several interesting characteristics to be discussed, although their low prevalence suggests that any conclusion should be

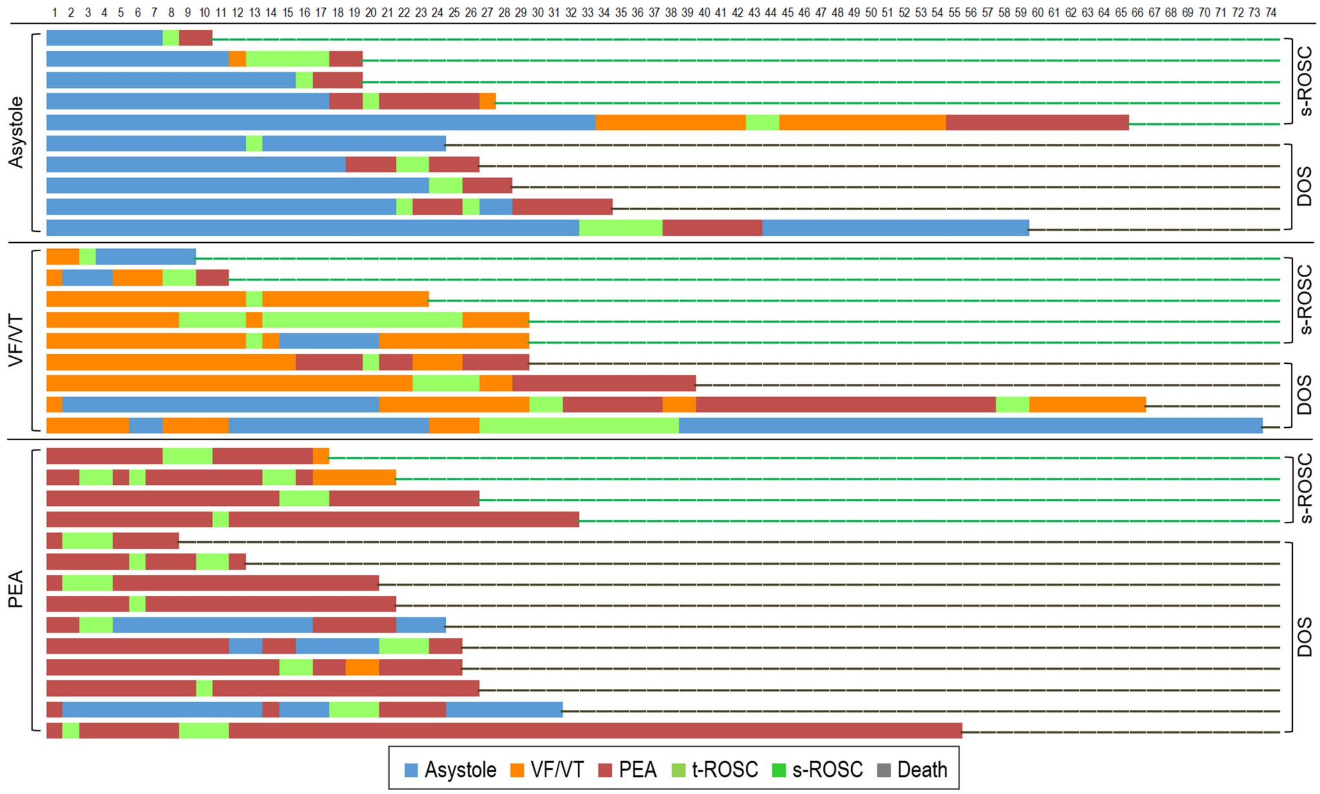

Figure 4. Sequences of state transitions over-time, stratified on presenting state, of patients who presented t-ROSC episodes during ALS. PEA: pulseless electrical activity; VF/VT: ventricular fibrillation/tachycardia. ROSC: return of spontaneous circulation. t-ROSC: transient ROSC. s-ROSC: stable ROSC. ALS: advanced life support. DOS: dead on scene.

considered with caution. We documented that t-ROSC states had very different lengths and were evenly distributed along the timeline. In most cases, t-ROSC was the status immediately following the presenting state and, although without statistical significance, this feature was observed more frequently (88% of cases) when PEA was the presenting state. Furthermore, initial PEA was associated with a less predictable temporal distribution of t-ROSCs. In patients having asystole as a presenting rhythm, the occurrence of t-ROSC states was associated with a higher probability of achieving s-ROSC. Skogvol et al. (5) found a circulatory deterioration into PEA in patients with late t-ROSC. Conversely, we observed that t-ROSC episodes tend to be intercalated between PEA states (Figure 4) and that PEA was the most frequently documented transition after a t-ROSC (Figure 3), suggesting in these circumstances a pseudo-PEA condition, as documented by TTI signal changes associated with the QRS complex. This finding, supported by previous studies (5–7), suggests that t-ROSC episodes and their duration during OHCA may be considered as a favorable prognostic factor by ALS teams, encouraging continuing resuscitative efforts. Unfortunately, recognizing ROSC only through pulse checking may be challenging. Industry should be solicited to develop methods for making feasible a real-time TTI analysis during resuscitation to quickly distinguish PEA from ROSC and avoid prolonged CPR interruptions. On the other side, other studies have analyzed the concept of "rearrest", i.e. a secondary cardiac arrest event after prehospital ROSC, that is often associated with poor longer term outcomes like survival to hospital discharge (32–36). However, these study considered rearrests occurred up to 1 year from OHCA, so that a comparison with our findings may be inappropriate. It would be interesting for future studies to investigate the long-term prognosis of patients presenting t-ROSCs during prehospital resuscitation.

Limitations

Some limitations of this study should be considered when interpreting our results. The study had an observational design, so that cause/effect relationships must be inferred with caution. Moreover, the study was carried out in a single emergency medical service center and enrolled a rather small population, so that a limited number of subjects were included in some presenting state subgroups. The analysis of the state transitions during CPR provided by laypersons or BLS teams was not included because of the unavailability of defibrillators with CPR events recording systems. Moreover, data on some OHCA events undergoing ALS during the study period were not available because a defibrillator different from that needed to record TTI and ECG traces was adopted during CPR. Finally, data on timing of drugs administration or advanced airway provision were not available, so that the potential association between ALS interventions and state transitions was not explored. Based on the above consideration, caution is needed in interpreting the study findings and in their generalization to the general population.

Conclusions

This study contributed to the understanding of the dynamic course of clinical state transitions during ALS in patients affected by OHCA. We observed that the initial state tends to be maintained over-time, so that presenting rhythm is the state with the higher probability to be found at a later time. Compared to asystole, VF/VT and PEA showed a higher propensity to change over-time. A stable and definitive ROSC was reached by 30 min of ALS in most cases, regardless of the presenting rhythm. In contrast, an unstable dynamics pattern continued longer in patients who were ultimately declared DOS.

Better knowledge about the dynamic course of clinical state transitions may providing a new theoretical framework to help conceptualizing cardiac arrest as an evolutionary process, integrating the classical ALS approach with separate algorithm panels for VF/VT, PEA, and asystole. More studies are needed to analyze in-depth the state transitions during the whole CPR efforts, also including that provided by laypersons or BLS teams. A larger spread of defibrillators and AEDs able to record ECG and TTI traces may contribute to improving the research on this topic. Furthermore, future research should consider other OHCA dimensions to better describe state transitions, including the QRS morphology and frequency in cases of PEA or the wave amplitude for VF/VT—assuming their prognostic potential, and relevant variables related both to the patient's characteristics and the quality of the resuscitation.

Disclosure Statement

No potential conflict of interest was reported by the author(s).

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