



Original Contribution

## Epinephrine administration in non-shockable out-of-hospital cardiac arrest☆



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### ABSTRACT

**Background:** Epinephrine is recommended for the treatment of non-shockable out of hospital cardiac arrest (OHCA) to obtain return of spontaneous circulation (ROSC). Epinephrine efficiency and safety remain under debate.

**Objective:** We propose to describe the association between the cumulative dose of epinephrine and the failure of ROSC during the first 30 min of advanced life support (ALS).

**Methodology:** A retrospective observational cohort study using the Paris SAMU 75 registry including all non-traumatic OHCA receiving epinephrine during the first 30 min of ALS were enrolled. Cumulative epinephrine dose given during ALS to ROSC was retrieved from medical reports.

**Results:** Among 1532 patients with OHCA, 776 (51%) had initial non-shockable rhythm. Fifty-four patients were excluded for missing data.

The mean value of cumulative dose of epinephrine was  $10 \pm 4$  mg in patients who failed to achieve ROSC (ROSC–) and  $4 \pm 3$  mg ( $p = 0.04$ ) for those who achieved ROSC.

ROC curve analysis indicated a cut-off point of 7 mg total cumulative epinephrine associated with ROSC– (AUC = 0.89 [0.86–0.92]).

Using propensity score analysis including age, sex and no-flow duration, association with ROSC– only remained significant for epinephrine > 7 mg ( $p \leq 10^{-3}$ , OR [CI95] = 1.53 [1.42–1.65]).

**Conclusion:** An association between total cumulative epinephrine dose administered during OHCA resuscitation and ROSC– was reported with a threshold of 7 mg, best identifying patients with refractory OHCA. We suggest using this threshold in this context to guide the termination of ALS and early decide on the implementation of extracorporeal life support or organ harvesting in the first 30 min of ALS.

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### 1. Introduction

Clinical practice on cardiopulmonary resuscitation (CPR) is regularly updated in the guidelines for basic life support (BLS) and advanced life support (ALS) which are published every 5 years by the American Heart Association or the European Resuscitation Council [1,2]. Despite recent progress, outcome after cardiac arrest (CA) remain poor, with survival rates between 8.2 and 22% and 6 to 11% for hospitalized and critically ill patients respectively [3–6]. Unfortunately, despite recommendations and progress of cares during the last 20 years, survival rate of out-of-hospital cardiac arrest (OHCA) do not overcome 10% [7,8]. Resuscitation failure constrains emergency medical services (EMS) dispatched to the scene to decide between the termination of ALS, the implementation of

extracorporeal life support (ECPR) in- or out-of-hospital, or organ donation after eligibility. In fact, a positive association was described between the early onset of ECPR and better outcomes in refractory OHCA [9].

The early objective of CPR is to obtain the return of spontaneous circulation (ROSC). The incidence of ROSC in OHCA varies from 30 to 80% in the literature [10–12]. Despite reported significant associations, the achievement of ROSC does not always predict long-term survival and the neurological outcome.

Initial shockable rhythms have a less pronounced association with time to obtain ROSC [9]. In case of asystole, epinephrine is recommended in association with CPR [13]. The duration of ALS remains under debate [14,15]. In France, refractory cardiac arrest is defined as the absence of ROSC after at least 30 min of normothermic CPR [15]. Negative effects of prolonged CPR and potential deleterious effects of epinephrine were observed [16–18].

To our knowledge, no study has focused on the cumulative dose of epinephrine associated with the failure to obtain ROSC during the first 30 min of ALS.

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## 2. Methods and patients

### 2.1. Methods

We conducted a retrospective analysis of out-of-hospital cardiac arrest (OHCA) registry data between January 1, 2007 and December 31, 2013 covering the whole population of Paris and involving all consecutive non-traumatic OHCA patients with resuscitation attempts.

All OHCA patients who required epinephrine administration by prehospital mobile intensive care units (MICU) dispatched to scene were enrolled in the study. The study population included patients over 18 years who underwent OHCA from either cardiac or non-cardiac aetiology, excluding traumatic causes. Patients older than 89 years were excluded considering the extremely bad prognosis and frequent early termination of CPR. Patients with missing data were excluded.

In France, the management of out-of-hospital emergencies is based on the emergency medical service, named SAMU (service d'aide médicale d'urgence). Identification of patients occurs through a phone call to the regulation call centre. When an OHCA is suspected, an emergency medical team (EMT) is dispatched to the scene, followed by a MICU.

No-flow duration corresponds to the time-lapse from collapse to the initiation of CPR and low-flow duration to the time from the initiation of CPR to ROSC.

Patients were categorized according to their initial rhythm: shockable rhythm (ventricular fibrillation and pulseless ventricular tachycardia) or non-shockable rhythm (pulseless electrical activity, asystole, and unclassified rhythms that were not shockable). ROSC was defined as a palpable pulse in any vessel.

All patients in the study were treated according to the 2005 and 2010 guidelines from the European Resuscitation Council [13,19,20] in their French-adjusted version [21,22].

Cumulative epinephrine dose given during ALS until ROSC was retrieved from medical reports.

Ethical approval for this study was provided by the local ethic committee. Based on the French law, the review board considered that consent of patients was waived for participation in this observational study.

### 2.2. Analysis

Receiver operating characteristic (ROC) curve analysis was used to determine the diagnosis performance of the cumulative epinephrine infusion for failure to obtain ROSC during the first 30 min of ALS. Analysis was stopped upon 30 min of ALS according to the French definition of refractory cardiac arrest [15].

We analysed the area under the curve (AUC) with a 95% confidence interval (CI) obtained after a resampling procedure based on a smoothed bootstrap due to the small size of the sample.

First, all variables for the primary outcome were analysed in a univariate model. Statistical significance of the variables was determined by Chi-square tests.

Then, a propensity score analysis including age, sex and no-flow duration was performed.

Data are presented as either absolute number (percentage), median with range or mean with standard deviation (SD).

Data analyses were performed using R<sup>®</sup> version 3.2.3.

## 3. Results

A total of 1532 patients with OHCA were included between January 1, 2007 and December 31, 2013. Among these patients, 776 (51%) had an initial non-shockable rhythm and 756 (49%) had an initial shockable rhythm (Fig. 1). Of the 776 patients, 54 patients had no available data on ROSC achievement and were excluded from the analysis. Table 1 gives an overview of the demographic and baseline clinical characteristics of patients with an initial non-shockable rhythm.

Among the 722 patients who had a non-shockable rhythm, 520 (72%) were male with a mean age of  $61 \pm 16$  years (range = 21–89). No patient had traumatic cardiac arrest or was over 89 years. Four-hundred and

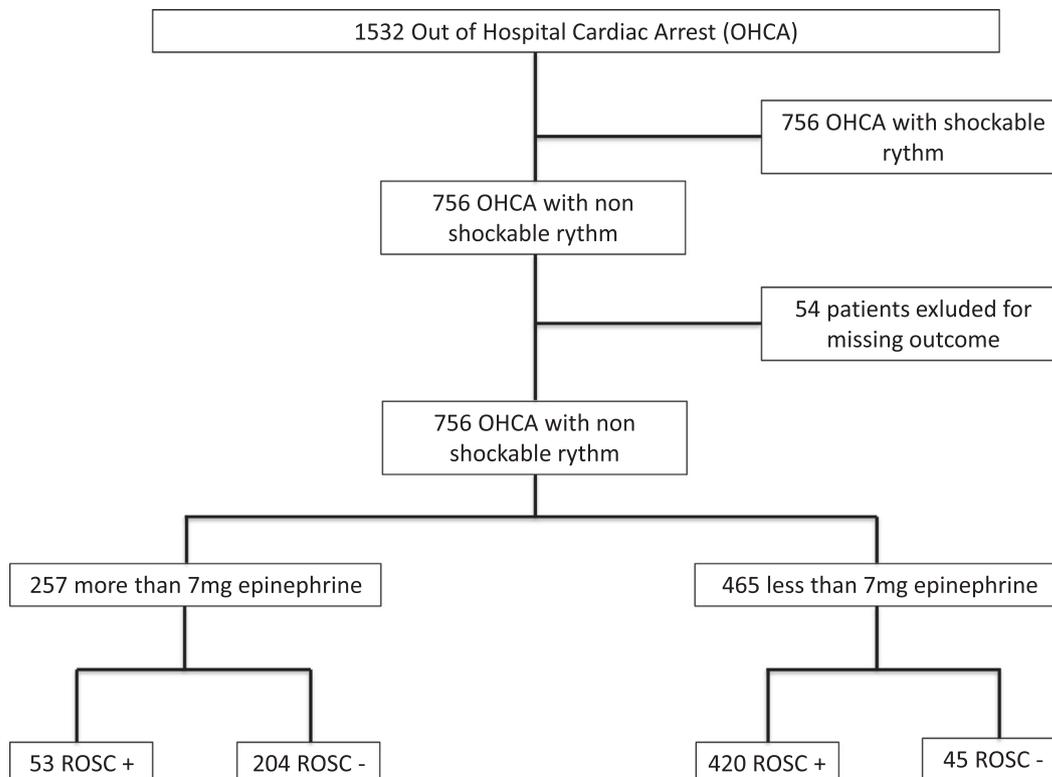


Fig. 1. Flow chart of the study.

**Table 1**

Demographics and clinical baseline characteristics of patients. The data are expressed as mean values with standard deviation ( $\pm$ SD) and as absolute numbers with percentage.

Mean age (years)	61 $\pm$ 16
Male gender n (%)	536 (69%)
No-flow (minutes)	6 $\pm$ 7
Low-flow (minutes)	19 $\pm$ 13
First observed end-tidal CO <sub>2</sub> (mm Hg)	36 $\pm$ 20

seventy-three patients (66%) achieved ROSC within the first 30 min of ALS (Table 2). The mean value of cumulative dose of epinephrine in the group of patients who failed to obtain ROSC (ROSC<sup>-</sup>) was 10  $\pm$  4 mg, compared to a mean cumulative dose of epinephrine of 4  $\pm$  3 mg ( $p = 0.04$ ) in the group of patients who achieved ROSC (ROSC<sup>+</sup>) (Table 2).

ROC curve analysis indicated a cut-off point of 7 mg epinephrine infusion for ROSC<sup>-</sup> patients in OHCA with initial non-shockable rhythms. The corresponding AUC was 0.89 [0.86–0.92].

The statistical relationship between the cumulative dose of epinephrine and ROSC was significant ( $p < 10^{-3}$ ). This association was found for both the delivery of less ( $p < 10^{-3}$ ) or more ( $p < 10^{-3}$ ) than 7 mg of total cumulative dose of epinephrine. To compensate for the confounding effect of covariates, a propensity score analysis, including age, sex and no-flow duration, found a remaining association with ROSC<sup>-</sup> only for a cumulative dose of epinephrine > 7 mg ( $p < 10^{-3}$ , OR [CI95] = 1.53 [1.42–1.65]).

#### 4. Discussion

Our study attempted to identify a parameter for early identification of patients who will fail to obtain ROSC during OHCA resuscitation with non-shockable rhythm. The dose of epinephrine is a parameter that can be obtained simply and quickly during cardiopulmonary resuscitation.

Non-shockable rhythm is the most common presentation of OHCA with an increasing incidence [23] and has a negative prognosis value [19]. Epinephrine administration is the main therapeutic of OHCA with non-shockable rhythm. However, its efficacy and safety remain under debate [24–29]. Considering the administration of 1 mg epinephrine every 4 min as recommended [1,2], 7 mg of epinephrine corresponds to the dose administered during 28 min of CPR. Interestingly, this time scale defines refractory CA [9]. Using this threshold, the AUC reached 89% to predict that patients who failed to obtain ROSC had received more than 7 mg epinephrine. Consequently, the AUC shows a probability of 11% to fail to obtain ROSC without having received more than 7 mg cumulative dose of epinephrine. Our work is a population study and lacks information on each individual. Our data found a high negative predictive value of 90% for ROSC failure using the cut-off of 7 mg epinephrine. However, the positive prediction value for ROSC failure when patients received >7 mg cumulative dose of epinephrine only reached 79%. This result suggests that a cumulative dose of epinephrine > 7 mg is not a sufficient criterion to decide to terminate ALS,

**Table 2**

Demographic characteristics of patients.

Data are expressed as mean value with minimal and maximal values and as absolute value with percentage.

	Dose of epinephrine during the first 30 min of resuscitation	
	>7 mg (n = 257)	≤7 mg (n = 465)
Age (years)	60 $\pm$ 16	62 $\pm$ 15
Gender (M:F)	184:73	336:129
ROSC + n (%)	53 (21%)	420 (90%)
ROSC - n (%)	204 (79%)	45 (10%)

implement extracorporeal life support or prepare for organ harvesting, as 20% patients achieved ROSC after they received >7 mg epinephrine. This decision is left to the physicians dispatched to the scene based on the patient's general condition, clinical examination, the gathered information on his medical history and the no-flow duration. However, at that point, it is possible to start considering an alternative to CPR.

Further studies should be carried to confirm these values, but also to evaluate the cumulative dose of epinephrine that best predicts neurological outcomes in determining cardiac arrest prognosis. We would expect a low number of ROSC failure when patients are administered less than 7 mg total epinephrine, unless CPR is terminated for contraindication (comorbidities, bad general condition) the most common being achievement of ROSC.

A recent study from Funada et al. [30] reported that only 0.23% OHCA patients with initial non-shockable rhythms who did not achieve ROSC in the prehospital setting had a cerebral performance category of 1–2 and that 1.1% survived. Recent studies highlighted the possibility to improve the prognosis of prolonged CA occurring both in-hospital [31] and out-of the hospital [32] when other measures such as ECPR are implemented early. [33]. The exact moment to terminate ALS or implement other measures remains unknown. Decision-making remains a teamwork based on many criteria as the initial rhythm, ROSC in the field, and patient's comorbidities. We suggest using the cumulated dose of epinephrine, as an early hallmark of poor outcome in OHCA with non-shockable rhythm to help the physician decide on alternatives in the case of refractory CA.

#### 4.1. Limitations

There are several limitations to this retrospective and registry-based study. Despite organization similarities in pre-hospital settings, differences in the management between medical teams may affect our results as therapeutics were left to the physician's discretion and bedside judgment.

No-flow and low-flow are well known prognosis factors [15]. We did not include low-flow durations in the analyses because we considered it as an equivalent of our outcome (ROSC). In this study, we didn't include data concerning ECPR candidates in non-shockable OHCA as we only focused the ROSC.

The definition of refractory cardiac arrest, i.e. the absence of ROSC after at least 30 min of normothermic cardiopulmonary resuscitation [15], is only used in France, limiting the use of our results in others countries. The herein results suggest that alternatives may be considered early, helped by the cumulative dose of received epinephrine. In France, in the context of refractory cardiac arrest, 3 options are considered: ECPR, organ donation or termination of ALS [15]. We did not take into account the aetiology of cardiac arrest, another prognosis factor of ROSC [15]. In this study, our interest was focused on short-term prognosis defined by ROSC and patients were not follow-up to evaluate long-term outcomes such as survival and neurological sequelae. Nonetheless, ROSC remains the first step toward survival and neurological recovery. Finally, we studied patients from one city only (Paris), where a MICU or an EMT needs an average of 9 min to reach a patient [34]. Extrapolating our results to other countries or hospital systems may be questioned because of the differences in the organisations of emergency medical systems.

#### 5. Conclusion

The cumulative dose of epinephrine during resuscitation of OHCA with non-shockable rhythms is associated with failure to obtain ROSC. We suggest that the cumulative dose of epinephrine may guide the physician terminate ALS or early decide on the implementation of extracorporeal life support or organ harvesting before 30 min of ALS.

Further prospective multicentre randomized studies are needed to validate this cut-off and assess a correlation between the cumulative

dose of epinephrine, or the duration of low-flow, and neurological outcomes to guide the management of OHCA and help establish an international definition for refractory cardiac arrest.

### Competing interests

All authors declare no competing interests.

### Authors' contribution

- Study concept and design: Jouffroy.
- Acquisition of data: Alexandre.
- Analysis and interpretation of data: Jouffroy.
- Drafting of the manuscript: Jouffroy, Saade.
- Critical revision of the manuscript for important intellectual content: Saade, Philippe, Carli, Vivien.

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