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Epinephrine versus norepinephrine in cardiac arrest patients with post-resuscitation shock

Wulfran Bougouin[1,2,3], Kaci Slimani[1,3], Marie Renaudier[1,3], Yannick Binois[1,3], Marine Paul[16], Florence Dumas[1,3,4,5], Lionel Lamhaut[1,3,4,6], Thomas Loeb[15], Sofia Ortuno[1,3,4,8], Nicolas Deye[9], Sebastian Voicu[9], Frankie Beganton[1,3], Daniel Jost[1,3,10], Armand Mekontso-Dessap[12,13,14], Eloi Marijon[1,3,4,7], Xavier Jouven[1,3,4,7], Nadia Aissaoui[1,3,4,8] and Alain Cariou[1,3,4,11*] on behalf of the Sudden Death Expertise Center Investigators

Abstract

Purpose: Whether epinephrine or norepinephrine is preferable as the continuous intravenous vasopressor used to treat post-resuscitation shock is unclear. We assessed outcomes of patients with post-resuscitation shock after out-of-hospital cardiac arrest according to whether the continuous intravenous vasopressor used was epinephrine or norepinephrine.

Methods: We conducted an observational multicenter study of consecutive patients managed in 2011–2018 for post-resuscitation shock. The primary outcome was all-cause hospital mortality, and secondary outcomes were cardiovascular hospital mortality and unfavorable neurological outcome (Cerebral Performance Category 3–5). A multivariate regression analysis and a propensity score analysis were performed, as well as several sensitivity analyses.

Results: Of the 766 patients included in five hospitals, 285 (37%) received epinephrine and 481 (63%) norepinephrine. All-cause hospital mortality was significantly higher in the epinephrine group (OR 2.6; 95%CI 1.4–4.7; $P=0.002$). Cardiovascular hospital mortality was also higher with epinephrine (aOR 5.5; 95%CI 3.0–10.3; $P<0.001$), as was the proportion of patients with CPC of 3–5 at hospital discharge. Sensitivity analyses produced consistent results. The analysis involving adjustment on a propensity score to control for confounders showed similar findings (aOR 2.1; 95%CI 1.1–4.0; $P=0.02$).

Conclusion: Among patients with post-resuscitation shock after out-of-hospital cardiac arrest, use of epinephrine was associated with higher all-cause and cardiovascular-specific mortality, compared with norepinephrine infusion. Until additional data become available, intensivists may want to choose norepinephrine rather than epinephrine for the treatment of post-resuscitation shock after OHCA.

Keywords: Out-of-hospital cardiac arrest, Post-resuscitation shock, Vasopressor therapy, Epinephrine, Norepinephrine

Introduction

Survival after out-of-hospital cardiac arrest (OHCA) remains about 10% [1, 2]. Although third of patients are admitted alive to the hospital [3], among them 50–70% die during the stay in the intensive care unit (ICU) [4, 5]. Most ICU deaths result from neurological injury or

*Correspondence: alain.cariou@cch.aphp.fr
[11] Medical Intensive Care Unit, AP-HP, Cochin Teaching Hospital, 27 rue du Faubourg Saint-Jacques, 75014 Paris Cedex 14, France
Full author information is available at the end of the article

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hemodynamic failure (including refractory shock and recurrent cardiac arrest) [4–6].

European [7] and American [8, 9] guidelines underline the crucial importance of hemodynamic optimization in patients with OHCA. The AHA guidelines point out that no head-to-head comparisons of vasopressors in OHCA are available [10], and the AHA stated recently that whether epinephrine or norepinephrine was better in cardiogenic shock remained unclear [11].

Several studies have compared epinephrine and norepinephrine in shock, usually due to sepsis [12–14], but found no significant difference in mortality. Similarly, a recent randomized controlled trial (RCT) in cardiogenic shock after myocardial infarction found no difference in overall mortality between the epinephrine and norepinephrine arms [15]. This study was not powered for mortality but was terminated early due to a higher incidence of refractory shock in the epinephrine arm. To the best of our knowledge, no study has specifically compared epinephrine and norepinephrine in patients with post-resuscitation shock. Epinephrine and norepinephrine are currently both considered as acceptable vasopressors in post-resuscitation shock, and choice of vasoactive drug is usually let at the discretion of physicians.

Here, we aimed to compare the association of epinephrine vs. norepinephrine use with the outcomes of patients admitted alive to the ICU with postresuscitation shock after successfully resuscitated OHCA.

Methods

This study is reported according to Stregthening The Reporting of Observational studies in Epidemiology guidelines [16].

Population and study setting

All cases of OHCA in the Paris metropolitan area (France) are included in the Sudden Death Expertise Center registry, which is described elsewhere [3, 17–20]. The appropriate ethics committees approved the registry (CNIL approval #912309 and CCTIRS approval #12336). In this registry, we identified all patients admitted alive after OHCA to any of five university hospitals (Cochin, Georges Pompidou Hospital, Lariboisière, Necker, and Henri Mondor) between 15 May 2011 and 15 May 2018. All hospitals are large university Hospitals, with high volume of admissions in ICU. Among them, patients with post-resuscitation shock were included in the study. Post-resuscitation shock was defined as a need for vasopressors for more than 6 h despite adequate fluid loading [21]. As recommended in international guidelines [7], management of post-resuscitation shock targeted a mean arterial pressure of 65 mmHg. Exclusion criteria were obvious extra-cardiac cause of cardiac arrest (trauma, drowning, drug overdose, electrocution, or asphyxia due to an external cause) [22], refractory cardiac arrest without sustainable return of spontaneous circulation (ROSC), refractory shock requiring extracorporeal membrane oxygenation (ECMO), absence of continuous intravenous treatment with epinephrine or norepinephrine, and continuous intravenous treatment with both epinephrine and norepinephrine. We performed an additional analysis including patients initially excluded because treated with both catecholamines.

Take-home message

Among patients with post-resuscitation shock after out-of-hospital cardiac arrest, use of epinephrine was associated with higher all-cause and cardiovascular-specific mortality, compared with norepinephrine infusion. Clinicians may consider that norepinephrine is preferable over epinephrine until the results of a randomized clinical trial become available.

Outcomes

The primary endpoint was all-cause mortality during the hospital stay. The secondary endpoints were cardiovascular-specific mortality, defined as either recurrent cardiac arrest or refractory hemodynamic shock [6]; and unfavorable neurological status at hospital discharge, defined as a Cerebral Performance Category score [23] of 3–5. A CPC level of 1 (good recovery) or 2 (moderate disability) was considered as favorable neurological outcome. A CPC level of 3 (severe disability), 4 (vegetative state), and 5 (death) were classified as unfavorable neurological status. We performed a sensitivity analysis using all-cause mortality during the ICU stay (instead of hospital stay). The patients who died of cardiovascular-specific mortality causes were compared to the patients with either other causes of death or discharged alive from the hospital, as reported previously [24]. We calculated the CAHP score, previously published, which includes 7 parameters (age, nonshockable rhythm, time from collapse to BLS, time from BLS-to-ROSC, location of cardiac arrest, epinephrine dose used during resuscitation, and arterial pH) and proved high discrimination value for prognosis after cardiac arrest. Formula of the CAHP score has been previously published [18].

Data collection

Data were collected using Utstein templates [25]. General data were recorded prospectively and included demographic characteristics and location of the OHCA (home vs. public place). Data on prehospital care included presence of a bystander, bystander cardiopulmonary resuscitation (CPR) before first-responder arrival, initial shockable rhythm before advanced life support, times

from collapse to CPR and from CPR to ROSC, and epinephrine use during resuscitation. The following data from the hospital stay were recorded: initial arterial pH at admission, initial blood lactate, whether coronary angiography was performed; myocardial dysfunction (defined as left ventricular ejection fraction below 40% at admission as measured using echocardiography), and renal replacement therapy during the ICU stay. We reported Inotropic Equivalent [26], defined as IE (μg/kg per/min) = dopamine + dobutamine + 100 × epinephrine + 100 × norepinephrine + 100 × isoproterenol + 15 × milrinone. Patients were classified in Epinephrine or Norepinephrine group, according to vasopressor used during ICU stay. Reasons for death were categorized as previously described by Witten et al. (recurrent cardiac arrest, refractory hemodynamic shock, brain death, withdrawal of life-sustaining treatment due to neurological impairments, withdrawal of life-sustaining treatments due to comorbidities, and respiratory failure) [6]. This categorization was performed by two of us (MR and YB) blinded from each other. In cases of divergent opinion on the reason for death, a third expert (WB) was asked to arbitrate.

Statistical analysis

Continuous data were described as mean ± SD or median [interquartile range], depending on distribution, and categorical data as number (percentage). Continuous variables were compared by applying Student's *t*-test, the Mann–Whitney test, or the Kruskal–Wallis test, as appropriate, and categorical variables were compared using the χ^2 test. We checked the linearity of continuous variables using fractional polynomial regression, and we dichotomized non-linear continuous variables based on the median.

To compare outcomes between patients treated with epinephrine infusion and norepinephrine infusion, we performed multivariate logistic regression after adjustment for factors known to affect OHCA outcomes (age, sex, bystander CPR, initial shockable rhythm, time from collapse to CPR, time from CPR to ROSC, epinephrine dose during resuscitation (before ROSC), arterial pH, myocardial dysfunction, targeted temperature management, percutaneous coronary intervention) [3, 17, 27, 28]. Sensitivity analyses using cardiovascular-specific mortality or unfavorable neurological outcome as the primary endpoint (instead of mortality) were performed. We also performed a sensitivity analysis after excluding moribund patients (defined as patients who died within 12 h of hospital admission). To take illness severity into account, we calculated the Cardiac Arrest Hospital Prognosis (CAHP) score [17, 18] for each patient then compared subgroups on either side of the median value (150). Finally, a sensitivity analysis was performed on the population that did not receive epinephrine before the ROSC.

A propensity analysis was performed to adjust for confounders, given the possibility of indication bias. A propensity score for continuous epinephrine use was developed based on pretreatment characteristics (initial rhythm, time from collapse to CPR, time from CPR to ROSC; arterial pH; myocardial dysfunction; recipient hospital). We then built a logistic regression model adjusted for the propensity score and also performed conditional logistic regression after 1:1 matching on the propensity score.

P values less than 0.05 were considered statistically significant. Only cases without missing data were included in the analysis. The statistical analysis was performed using STATA software version v15.1 (Lakeway Drive, TX).

Results

From May 15, 2011, to May 15, 2018, 1421 patients with OHCA followed by post-resuscitation shock were admitted to the five participating ICUs (Fig. 1). After exclusion of patients who had refractory cardiac arrest, received ECMO, or received neither or both continuous intravenous epinephrine and norepinephrine, 766 patients were left for our study. Of these 766 patients, 481 (63%) were treated with norepinephrine, and 285 (37%) with epinephrine. Regarding data collection, inter-rater agreement proved excellent (kappa = 0.87).

Baseline characteristics

Table 1 reports the main baseline features in the two study groups. Median age was 64 years (IQR 52–75), and 560/766 (73%) patients were male. Median time from collapse to CPR was 5 min (IQR 1–10) and from CPR to ROSC 22 min (IQR 15–30). All patients were on mechanical ventilation, and sedated. Patients treated with continuous intravenous epinephrine less often had an initial shockable rhythm and had a longer time from CPR to ROSC. At admission, patients treated with epinephrine had lower blood pressure and higher lactate, with higher heart rate (HR 95/min vs 90/min, $P = 0.02$), as compared with patients treated with norepinephrine. Diastolic blood pressure did not differ. Lactate was higher at admission, and remained higher during the first hours, among patients treated with epinephrine. They also had a lower arterial pH at admission and a higher prevalence of myocardial dysfunction. Few of them underwent coronary angiography and targeted temperature management. During the first 48 h of ICU, in the adrenaline group, maximal dose was 0.7 microg/kg/min (median), IQR 0.3–1.9, whereas in the noradrenaline group, maximal dose was 0.6 microg/kg/min (median), IQR 0.3–1.4.

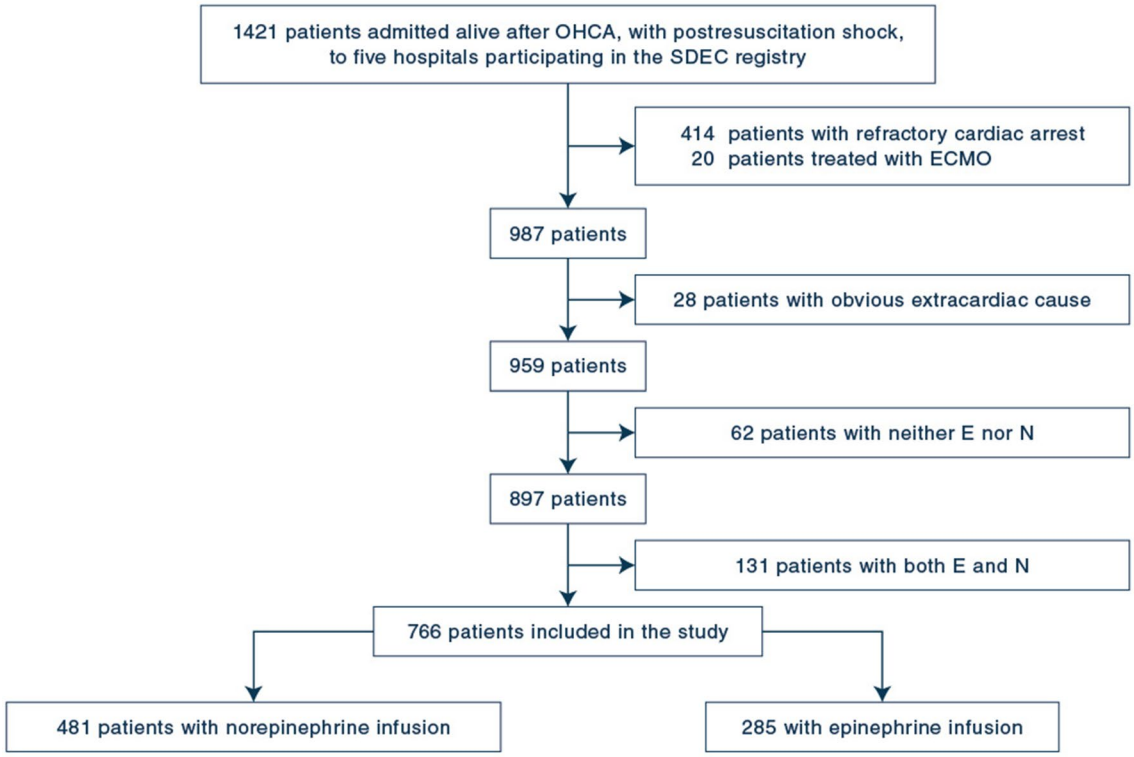

Fig. 1 Patient flowchart. E, epinephrine; N, norepinephrine

Duration of catecholamine support did not significantly differ in the first 48 h, 24 h in median in epinephrine group (IQR 12–48), vs 30 h in norepinephrine group (IQR 19–48), $P=0.28$.

Outcomes

Overall, 235/766 patients survived to hospital discharge (31%). The neurological outcome was favorable in 212 (98%, 18 with missing data). Among the 531 patients who died during the hospital stay, 133 (27%) died from refractory hemodynamic shock and 36 (7%) from recurrent cardiac arrest. Early recurrent cardiac arrest (in the first 48 h) was more frequent in patients treated with adrenaline (7%) than patients treated with noradrenaline (2%), $P<0.001$. Thus, 169 (34%) patients died of cardiovascular causes, whereas 211 (40%) died after withdrawal of life-sustaining treatments due to neurological impairments. Median delay before death from withdrawal of life-sustaining treatments was 7 days (IQR 4–9 days). The next most common cause of death was brain death, with 58 (11%) patients. All-cause mortality and cardiovascular-specific mortality are reported in Fig. 2.

By univariate analysis, patients treated with epinephrine infusion had higher all-cause mortality during the hospital stay (83% vs. 61%, $P<0.001$), including more deaths from refractory shock (35% vs. 9%, $P<0.001$) and recurrent cardiac arrest (9% vs. 3%, $P<0.001$), translating into higher cardiovascular-specific mortality (44% vs. 11%, $P<0.001$); as well as a lower frequency of favorable neurological outcomes (15% vs. 37%, $P<0.001$), compared with the patients treated with norepinephrine.

Table 2 reports the findings from the univariate analysis comparing patients who were and were not discharged alive from the hospital. By adjusted multivariable analysis (Table 3), epinephrine infusion was independently associated with all-cause mortality (odds ratio [OR] 2.6, 95%CI 1.4–4.7, $P=0.002$). Sensitivity analysis performed (after exclusion of moribund patients, restricted to patients with a CAHP score < 150, restricted to patients with a CAHP score > 150, or after exclusion of patients treated with epinephrine before ROSC) found consistent results.

Similar results were found when considering the association with cardiovascular mortality (adjusted OR [aOR] 5.5, 95%CI 3.0–10.3, $P<0.001$), with ICU mortality (aOR 2.5 95%CI 1.4–4.4, $P=0.003$) or with an unfavorable neurological outcome (CPC 3–5 at hospital discharge: aOR 3.0, 95%CI 1.6–5.7, $P=0.001$). Results across subgroups (shockable rhythms, cardiac cause of OHCA) were consistent. No significant interaction with date of OHCA was found. Analysis including patients treated with both

Table 1 Utstein characteristics and ICU management of patients according to epinephrine or norepinephrine infusion use (*N* = 766)

Baseline characteristics	All patients *N* = 766	Norepinephrine *N* = 481	Epinephrine *N* = 285	*P* value
Male, *n* (%)	560 (73)	356 (74)	204 (72)	0.46
Mean age (SD)	63 (15)	63 (15)	64 (16)	0.40
Previous coronary artery disease, *n* (%)	155 (21)	92 (20)	63 (23)	0.26
Occurrence at home, *n* (%)	400 (52)	229 (48)	171 (60)	0.001
Witnessed, *n* (%)	688 (90)	438 (91)	250 (88)	0.14
Bystander CPR before EMS arrival, *n* (%)	489 (71)	316 (72)	173 (69)	0.31
Initial shockable rhythm, *n* (%)	400 (52)	276 (57)	124 (44)	< 0.001
Time from CA to CPR, median (IQR)	5 (1–10)	4 (1–8)	5 (0–10)	0.22
Time from CPR to ROSC, median (IQR)	22 (15–30)	20 (13–29)	25 (17–35)	< 0.0001
Systolic Blood Pressure at admission, median (IQR)	120 (99–145)	123 (101–143)	118 (91–146)	0.02
Mean Arterial Pressure at admission, median (IQR)	87 (71–104)	89 (73–105)	86 (69–103)	0.03
Diastolic Blood Pressure at admission, median (IQR)	68 (55–83)	70 (55–83)	68 (54–81)	0.41
pH at admission, median (IQR)	7.21 (7.10–7.29)	7.23 (7.14–7.31)	7.17 (7.03–7.26)	< 0.0001
Arterial lactate at admission, median (IQR)	5.8 (3.2–9.8)	4.8 (2.7–8.3)	7.6 (4.7–12)	0.0001
Second lactate in the first 12 h, median (IQR)	3 (1.7–6.5)	2.4 (1.4–4.4)	6.7 (3.5–9)	0.0001
Lactate clearance at 12th hour, %, median (IQR)	35 (2–60)	47 (18–64)	13 (– 21–37)	< 0.0001
Maximal Heart Rate in the first 48 h, mean (SD)	132 (36)	134 (36)	128 (34)	0.15
Inotropic equivalent, median (IQR)	56 (28–125)	49 (25–103)	68 (33–187)	0.003
Initial Left Ventricular Ejection Fraction, %, mean (SD)	40 (15)	42 (15)	35 (15)	0.0003
Myocardial dysfunction, *n* (%)	389 (62)	229 (57)	160 (72)	< 0.001
Coronary angiogram, *n* (%)	595 (78)	409 (85)	186 (66)	< 0.001
Renal replacement therapy in ICU, *n* (%)	228 (31)	140 (30)	88 (32)	0.49
Targeted temperature management, *n* (%)	533 (71)	406 (85)	127 (47)	< 0.001

ICU intensive care unit, *CPR* cardiopulmonary resuscitation, *EMS* emergency medical service, *CA* cardiac arrest, *IQR* interquartile range, *ROSC* return of spontaneous circulation, *SD* standard deviation

vasopressors found consistent results (Electronic Supplementary Material).

Propensity-score analysis

The logistic model in which available covariates were used to develop a propensity score for receiving an epinephrine infusion yielded a C statistic of 0.85 (95%CI 0.82–0.89). After adjustment on the propensity score and on other prognostic variables not included in the propensity score (age, sex, bystander CPR, epinephrine dose during CPR, targeted temperature management, and percutaneous coronary intervention), receiving a continuous intravenous epinephrine infusion was significantly associated with all-cause mortality (OR 2.1, 95%CI 1.1–4.0, $P = 0.02$). Similar results were found for cardiovascular-specific mortality (aOR 4.3, 95%CI 2.2–8.3, $P < 0.001$). We also performed a conditional logistic regression analysis of 93 pairs matched on a score for all-cause mortality. In this analysis, continuous intravenous epinephrine infusion was associated, albeit non-significantly, with all-cause mortality (OR 1.8; 95%CI 0.94–3.4; $P = 0.08$). The association with cardiovascular-specific mortality was statistically significant (OR 3.4, 95%CI 1.7–6.8, $P = 0.001$).

Discussion

In this large population-based study of 766 patients admitted alive to five French hospitals after OHCA followed by post-resuscitation shock, continuous epinephrine infusion was used in 37% of patients. Overall, 69% of patients died before hospital discharge, and one-third of deaths were due to cardiovascular causes. The use of a continuous intravenous epinephrine infusion was associated with significant increases in both all-cause and cardiovascular mortality, compared to the use of norepinephrine. This association was robust in various populations and with multiple methodological approaches. Although our study design cannot provide proof of causality, our results obtained in the largest cohort to date of patients with post-resuscitation shock after OHCA provide strong suggestive evidence for choosing the vasoactive medication used.

Epinephrine may increase the risk of arrhythmia and recurrent cardiac arrest [29], the severity of

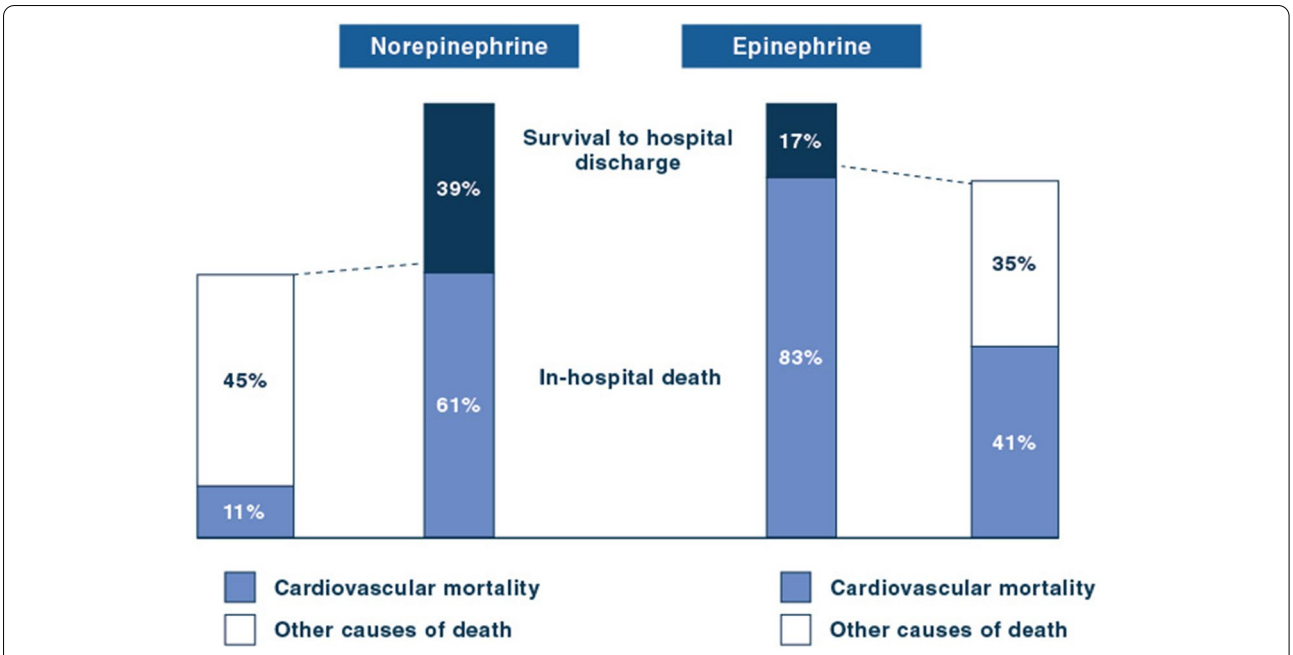

Fig. 2 Short-term survival of patients according to vasopressor used. Among patients treated with norepinephrine, 61% died in hospital (11% from cardiovascular causes, 45% from other causes of death, 5% missing causes of death). Among patients treated with epinephrine, 83% died in hospital (41% from cardiovascular causes, 35% from other causes of death, 7% missing causes of death)

Table 2 Factors associated with survival to hospital discharge

Baseline characteristics	Survivors ($n=235$)	Non-survivors ($n=526$)	*P* value
Male, *n* (%)	183 (78)	373 (71)	0.05
Age, mean (SD)	59 (16)	65 (15)	< 0.0001
Bystander CPR, *n* (%)	180 (82)	304 (66)	< 0.001
Initial shockable rhythm, *n* (%)	195 (83)	201 (38)	< 0.001
No-flow > 5 min, *n* (%)	80 (36)	264 (57)	< 0.001
Low-flow > 22 min, *n* (%)	70 (31)	293 (59)	< 0.001
Epinephrine dose before ROSC, mean (SD)	1.3 (2.3)	3.5 (3.2)	< 0.001
Initial pH > 7.21	164 (71)	208 (42)	< 0.001
Percutaneous coronary intervention, *n* (%)	104 (47)	118 (29)	< 0.001
Targeted temperature management, *n* (%)	190 (83)	338 (66)	< 0.001
Myocardial dysfunction, *n* (%)	137 (64)	250 (62)	0.50
Epinephrine infusion, *n* (%)	49 (21)	236 (45)	< 0.001

CPR cardiopulmonary resuscitation, *ROSC* return of spontaneous circulation, *SD* standard deviation

post-resuscitation myocardial dysfunction [30], and the severity of post-resuscitation shock [31]. Experimental studies suggest detrimental effects of epinephrine on myocardial function that may stem from a mismatch between oxygen consumption and supply [29]. Given the known cardiovascular effects of epinephrine, we assessed not only all-cause mortality but also cardiovascular mortality (including refractory hemodynamic shock and sudden cardiac death, as previously defined [6]). We found consistent results with a significant association between epinephrine use after ROSC and sudden death, refractory shock, and the combination of both.

Post-resuscitation shock occurs in 50–70% of patients after OHCA [4, 5, 32] and was first described half a century ago [33–35]. This post-cardiac arrest syndrome is a model of mixed shock. Initially, patients develop myocardial dysfunction, which is usually reversible [36] (hence the term "myocardial stunning" [37]). Then,

Table 3 Models used to assess the association between epinephrine infusion and outcomes

	OR	95% CI	*P* value
All-cause mortality			
Crude association	3.1	2.2–4.4	< 0.001
Multivariable regression*	2.6	1.4–4.7	0.002
Multivariable regression* after exclusion of moribund patients	2.4	1.3–4.4	0.007
Adjustment on propensity score¶	2.1	1.1–4	0.02
Conditional logistic regression after matching on the propensity score	1.8	0.94–3.4	0.08
Multivariable regression* in patients with			
CAHP score < 150 (predicted favorable outcome)	2.3	1.1–4.9	0.03
CAHP score > 150 (predicted poor outcome)	3.4	1.1–10.5	0.03
Cardiovascular-specific mortality			
Crude association	6.2	4.2–9	< 0.001
Multivariable regression*	5.5	3–10.3	< 0.001
Multivariable regression* after exclusion of moribund patients	5.6	2.6–12.1	< 0.001
Adjustment on propensity score¶	4.3	2.2–8.3	< 0.001
Conditional logistic regression after matching on the propensity score	3.4	1.7–6.8	0.001
Unfavorable neurologic outcome (CPC 3, 4, 5) at hospital discharge			
Crude association	3.4	2.4–5	< 0.001
Multivariable logistic regression*	3	1.6–5.7	0.001

OR odds ratio, *95%CI* 95% confidence interval, *CAHP* Cardiac Arrest Hospital Prognosis, *CPC* Cerebral Performance Category

*Logistic regression adjusted for sex, age, bystander CPR, initial shockable rhythm, time from collapse to CPR > 5 min; time from CPR to ROSC > 22 min, epinephrine dose during resuscitation (before ROSC), arterial pH > 7.21, myocardial dysfunction, targeted temperature management, and percutaneous coronary intervention

¶ Adjusted on propensity score, age, sex, bystander CPR, epinephrine dose during CPR, targeted temperature management, and percutaneous coronary intervention

ischemia–reperfusion syndrome commonly leads to vasoplegia. These two components are similar to those involved in septic shock, and the immuno-inflammatory profile of patients with post-resuscitation shock resembles sepsis-related systemic inflammatory response syndrome [38]. In the setting of cardiogenic shock, a pilot RCT found no significant difference in survival between 15 patients given epinephrine and 15 given norepinephrine [39]. A more recent RCT in 57 patients with cardiogenic shock following myocardial infarction demonstrated no difference in mortality (a secondary outcome) between the epinephrine and norepinephrine groups [15]. In the field of cardiac arrest, optimization of hemodynamic status might be useful to improve prognosis. Accordingly, two recent RCTs (NEUROPROTECT [40] and COMACARE [41]) assessed goal-directed hemodynamic management and low-normal vs. high-normal mean arterial pressure after OHCA, respectively, and found no differences in the primary outcome (extent of anoxic brain damage and neuron-specific enolase levels, respectively). Of note, a pooled analysis of these two trials showed that the extent of myocardial injury was less in patients kept at a high-normal mean arterial pressure using inotropes and vasopressors [42]. Thus, in both septic shock and cardiogenic shock, no convincing evidence points to either epinephrine or norepinephrine as the better vasopressor [43, 44]. Recent European guidelines [7] underlined the lack of evidence regarding the choice of vasoactive drugs for post-cardiac arrest patients. To the best of our knowledge, our study is the first to report an association between continuous intravenous epinephrine after ROSC and both overall mortality and cardiovascular mortality in patients with post-resuscitation shock. Levy et al., and our study, provided evidence that norepinephrine might be preferable over epinephrine in post-resuscitation shock.

In our study, the groups treated with epinephrine vs. norepinephrine exhibited several differences. Several risk factors for poorer outcomes were more common in the epinephrine group, such as unshockable rhythm, longer time from CPR to ROSC, lower blood pH at admission, and myocardial dysfunction. However, we performed several analyses to mitigate the effect of these confounders. The association between epinephrine and higher mortality persisted after the exclusion of moribund patients and in both CAHP score groups (with scores < 150 indicating a better prognosis and higher scores a worse prognosis). This association was also found in the multivariable regression analysis and after adjustment on a propensity score. Overall, the size of our population, which is the largest reported to our knowledge, its multicenter design with the inclusion of consecutive patients, and the

consistency of the results in various analyses add credibility to our results. In our study, vasopressor needs were high (maximal dose in the adrenaline group 0.7 microg/kg/min, and maximal dose in the noradrenaline group 0.6 microg/kg/min), higher than previously described in Laurikkala et al. [45] As compared with this previous study, our population had several characteristics associated with the severity of post-resuscitation shock (longer time to ROSC, lower rate of shockable rhythm, higher rates of targeted temperature management and sedation), which might explain the higher vasopressor requirements.

We must acknowledge several limitations. First, our design is observational and therefore does not allow definitive conclusions about causality. Second, we cannot exclude an indication bias regarding the use of epinephrine. However, the propensity score analysis that took this potential bias into account produced consistent results. Third, the administration of epinephrine before the ROSC may act as a confounder, as it may have deleterious effects. Nevertheless, our analysis restricted to patients without epinephrine use before the ROSC found similar results. Fourth, we were not able to assess a potential dose effect of epinephrine.

Conclusion

In our population-based study including 766 patients with post-resuscitation shock, a third of patients received continuous intravenous epinephrine after the ROSC. This use of epinephrine was associated with higher all-cause and cardiovascular-specific mortality, compared with norepinephrine infusion, in analyses using various methodological approaches. Additional data could be useful to assess the optimal vasopressor for patients with post-resuscitation shock. Until such data become available, intensivists may want to choose norepinephrine rather than epinephrine for the treatment of post-resuscitation shock after OHCA.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-021-06608-7.

Abbreviations

AHA: American Heart Association; CAHP: Cardiac Arrest Hospital Prognosis; CPR: Cardiopulmonary resuscitation; ECMO: Extracorporeal membrane oxygenation; OHCA: Out-of-hospital cardiac arrest; OR: Odds ratio; RCT: Randomized controlled trial; ROSC: Return of spontaneous circulation.

Author details

[1] Paris Cardiovascular Research Center (PARCC), INSERM Unit 970, Paris, France. [2] Ramsay Générale de Santé, Hôpital Privé Jacques Cartier, Massy, France. [3] Paris Sudden Death Expertise Center, Paris, France. [4] Université de Paris, Paris, France. [5] Emergency Department, Cochin-Hotel-Dieu Hospital, APHP, Paris, France. [6] Intensive Care Unit and SAMU 75, Necker Enfants-Malades Hospital, Paris, France. [7] Cardiology Department, Georges Pompidou European Hospital, AP-HP, Paris, France. [8] Medical ICU, Georges Pompidou European Hospital, AP-HP, Paris, France. [9] Medical ICU, Lariboisière Hospital, AP-HP, Paris, France. [10] Brigade de Sapeurs Pompiers de Paris (BSPP), Paris, France. [11] Medical Intensive Care Unit, AP-HP, Cochin Teaching Hospital, 27 rue du Faubourg Saint-Jacques, 75014 Paris Cedex 14, France. [12] Service de Médecine Intensive Réanimation, AP-HP, Hôpitaux Universitaires Henri Mondor, 94010 Créteil, France. [13] Faculté de Santé, Université Paris Est Créteil, Groupe de recherche clinique CARMAS, 94010 Créteil, France. [14] INSERM U955, Université Paris-Est Créteil, Créteil, France. [15] SAMU des Hauts-de-Seine, APHP – Université Paris-Saclay, Hôpital Raymond Poincaré, 92 380 Garches, France. [16] Intensive Care Unit, Mignot Hospital, Le Chesnay, France.

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List of Paris Sudden Death Expertise Center investigators

F. Adnet, AP-HP, Paris 13 University, Avicenne Hospital, Emergency Medical Services (SAMU) 93, Bobigny, France. J. M. Agostinucci, AP-HP, Paris 13 University, Avicenne Hospital, Emergency Medical Services (SAMU) 93, Bobigny, France. N. Aissaoui-Balanant, AP-HP, Georges Pompidou European Hospital, Medical Intensive Care Unit, Paris, France. V. Algalarrondo, AP-HP, Antoine Beclere University Hospital, Department of Cardiology, Clamart, France. F. Alla, French National Health Insurance (CNAMTS), Paris, France. C. Alonso, Clinique Ambroise Paré, Department of Cardiology, Neuilly, France. W. Amara, Hospital Group of Montfermeil – Le Raincy, Department of Cardiology, Montfermeil, France. D. Annane, AP-HP, INSERM U1173 (Laboratory of Inflammation and Infection), University of Versailles—Saint Quentin en Yvelines, Raymond Poincare Hospital, General Intensive Care Unit, Garches, France. C. Antoine, Biomedecine agency, Saint-Denis-la-Plaine, France. P. Aubry, AP-HP, Bichat Hospital, Department of Cardiology, Paris, France. E. Azoulay, AP-HP, Paris Diderot Sorbonne University, Saint Louis Hospital, Medical Intensive Care Unit, Paris, France. F. Beganton, INSERM U970—PARCC, Paris, France. C. Billon, AP-HP, Georges Pompidou European Hospital, Department of Genetic, Paris, France. W. Bougouin, Private Hospital Jacques Cartier, Medical Intensive Care Unit, Massy, France. J. Boutet, AP-HP, Raymond Poincare Hospital, Emergency Medical Services (SAMU) 92, Garches, France. C. Bruel, Saint Joseph Hospital, Medical-Surgical Intensive Care Unit, Paris, France. P. Bruneval, AP-HP, Georges Pompidou European Hospital, Pathology Department, Paris, France. A. Cariou, AP-HP, Cochin Hospital, Medical Intensive Care Unit, Paris, France. P. Carli, AP-HP, Paris Descartes University, Necker—Enfants Malades Hospital, Emergency Medical Services (SAMU) 75, Intensive Care Unit, Paris, France. E. Casalino, AP-HP, Emergency Medical Services (SAMU) 92, Clichy, France. C. Cerf, Foch Hospital, Intensive Care Unit, Suresnes, France. A. Chaib, Andre Gregoire Hospital, Department of Cardiology, Montreuil, France. B. Cholley, AP-HP, Georges Pompidou European Hospital, Department of Anaesthesia and Surgical Intensive Care Medicine, Paris, France. Y. Cohen, AP-HP, Avicenne Hospital, Medical-Surgical Intensive Care Unit, Bobigny, France. A. Combes, AP-HP, Pitié-Salpetriere Hospital, Cardiology Institute (ICAN), Intensive Care Unit, Paris, France. J. M. Coulaud, CHI Montfermeil, Intensive Care Unit, France. M. Crahes, AP-HP, Georges Pompidou European Hospital, Pathology Department, Paris, France. D. Da Silva, Delafontaine Hospital, Intensive Care Unit, Saint-Denis, France. V. Das, Andre Gregoire Hospital, Medical-Surgical Intensive Care Unit, Montreuil, France. A. Demoule, AP-HP, Pitie Salpetriere Hospital, Medical Intensive Care Unit and Respiratory Division, Paris, France. I. Denjoy, AP-HP, Bichat Hospital, Department of Cardiology, Paris, France. N. Deye, AP-HP, Lariboisiere Hospital, Intensive Care Unit, Paris, France. J. L. Diehl, AP-HP, Georges Pompidou European Hospital, Medical Intensive Care Unit, Paris, France. S. Dinanian, AP-HP, Antoine Beclere Hospital, Department of Cardiology, Clamart, France. L. Domanski, Brigade de Sapeurs Pompiers de Paris (BSPP), Paris, France. D. Dreyfuss, AP-HP, Louis Mourier Hospital, Intensive Care Unit, Colombes, France. D. Duboc, AP-HP, Cochin Hospital, Department of Cardiology, Paris, France. J. L. Dubois-Rande, AP-HP, Henri Mondor Hospital, Department of Cardiology, Creteil, France. F. Dumas, AP-HP, Cochin Hospital, Department of Emergency, Paris, France. J. Duranteau, AP-HP, Bicetre Hospital, Department of Anaesthesia and Intensive Care Medicine, Le Kremlin-Bicetre, France. J. P. Empana, INSERM U970—PARCC, Paris, France. F. Extramiana, AP-HP, Bichat Hospital, Department of Cardiology, Paris, France. J. Y. Fagon, AP-HP, Georges Pompidou European Hospital, Intensive Care Unit, Paris, France. M. Fartoukh, AP-HP, Sorbonne University (Paris 6), Tenon Hospital, Intensive Care Unit, Paris, France. F. Fieux, CHI Montfermeil, Intensive Care Unit, France. M. Gabbas, French National Health Insurance (CNAMTS), Paris, France. E. Gandjbakhch, AP-HP, Pitie-Salpetriere

Hospital, Cardiology Institute (ICAN), Department of Cardiology, Paris, France. G.Geri, AP-HP, Ambroise Pare Hospital, Intensive Care Unit, Boulogne-Billancourt, France. B. Guidet, AP-HP, Sorbonne University (Pierre et Marie Curie University – Paris 6), Saint Antoine Hospital, Intensive Care Unit, Paris, France. F. Halimi, Private Hospital of Parly 2, Department of Cardiology, Le Chesnay, France. P. Henry, AP-HP, Sorbonne Paris Cite University (Paris Diderot University), Lariboisiere Hospital, Department of Cardiology, Paris, France. F. Hidden Lucet, AP-HP, Pitie-Salpetriere Hospital, Cardiology Institute (ICAN), Department of Cardiology, Paris, France. P. Jabre, INSERM U970 – PARCC, Emergency Medical Services (SAMU) 75, Paris, France. L. Joseph, Bicetre Hospital, Transplant Coordination, Le Kremlin-Bicetre, France. D. Jost, Brigade de Sapeurs Pompiers de Paris (BSPP), Paris, France. X. Jouven, AP-HP, Georges Pompidou European Hospital, Department of Cardiology, Paris, France. N. Karam, AP-HP, Georges Pompidou European Hospital, Department of Cardiology, Paris, France. H. Kassim, INSERM U970—PARCC, Paris, France. J. Lacotte, Private Hospital Jacques Cartier, Department of Cardiology, Massy, France. K. Lahlou-Laforet, AP-HP, Georges Pompidou European Hospital, Department of Psychiatry, Paris, France. L. Lamhaut, AP-HP, Paris Descartes University, Necker—Enfants Malades Hospital, Emergency Medical Services (SAMU) 75, Intensive Care Unit, Paris, France. A. Lanceleur, Foch Hospital, Intensive Care Unit, Suresnes, France. O. Langeron, AP-HP, Pitie-Salpetriere Hospital, Department of Anaesthesia and Surgical Intensive Care Medicine, Paris, France. T. Lavergne, AP-HP, Georges Pompidou European Hospital, Department of Cardiology, Paris, France. E. Lecarpentier, AP-HP, Henri Mondor Hospital, Emergency Medical Services (SAMU) 94, Creteil, France. A. Leenhardt, AP-HP, Bichat Hospital, Department of Cardiology, Paris, France. N. Lellouche, AP-HP, Henri Mondor Hospital, Department of Cardiology, Creteil, France. V. Lemiale, AP-HP, Paris Diderot University, Saint Louis Hospital, Medical Intensive Care Unit, Paris, France. F. Lemoine, Brigade de Sapeurs Pompiers de Paris (BSPP), Paris, France. F. Linval, AP-HP, Paris 13 University, Avicenne Hospital, Emergency Medical Services (SAMU) 93, Bobigny, France. T. Loeb, AP-HP, Raymond Poincare Hospital, Emergency Medical Services (SAMU) 92, Garches, France. B. Ludes, Institute of Legal Medicine, Paris Descartes University, Paris, France. C. E. Luyt, AP-HP, Pitie-Salpetriere Hospital, Cardiology Institute (ICAN), Intensive Care Unit, Paris, France. A. Maltret, AP-HP, Necker—Enfants Malades Hospital, Department of Pediatric Cardiology, Paris, France. N. Mansencal, Ambroise Pare Hospital, Department of Cardiology, Boulogne-Billancourt, France. N. Mansouri, AP-HP, Henri Mondor Hospital, Emergency Medical Services (SAMU) 94, Creteil, France. E. Marijon, AP-HP, Georges Pompidou European Hospital, Department of Cardiology, Paris, France. J. Marty, AP-HP, Henri Mondor Hospital, Emergency Medical Services (SAMU) 94, Creteil, France. E. Maury, AP-HP, Sorbonne University (Pierre et Marie Curie University – Paris 6), Saint Antoine Hospital, Intensive Care Unit, Paris, France. V. Maxime, AP-HP, Raymond Poincare Hospital, General Intensive Care Unit, Garches, France. B. Megarbane, AP-HP, Lariboisiere Hospital, Intensive Care Unit, Paris, France. A. Mekontso-Dessap, AP-HP, DHU A-TVB, CARMAS Research Group, Henri Mondor Hospital, Intensive Care Unit, Creteil, France. H. Mentec, Victor Dupouy Hospital, Intensive Care Unit, Argenteuil, France. J. P. Mira, AP-HP, Cochin Hospital, Medical Intensive Care Unit, Paris, France. X. Monnet, AP-HP, Bicetre Hospital, Medical Intensive Care Unit, Le Kremlin-Bicetre, France. K. Narayanan, INSERM U970—PARCC, Paris, France. N. Ngoyi, AP-HP, Paris 7 University, Beaujon Hospital, Emergency Medical Services (SAMU) 92, Clichy, France. M. C. Perier, INSERM U970—PARCC, Paris, France. O. Piot, Centre Cardiologique du Nord, Department of Cardiology, Saint-Denis, France. R. Pirracchio, AP-HP, Georges Pompidou European Hospital, Intensive Care Unit, Paris, France. P. Plaisance, Emergency Medical Services (SAMU) 75, Lariboisière SMUR, Paris, France. B. Plaud, AP-HP, Saint Louis Hospital, Department of Anaesthesia and Surgical Intensive Care Medicine, Paris, France. I. Plu, AP-HP, Pitie-Salpetriere Hospital, Neuropathology Escourolle, Paris, France. J. H. Raphalen, AP-HP, Necker—Enfants Malades Hospital, Intensive Care Unit, Paris, France. M. Raux, AP-HP, Pitié Salpétrière Hospital, Department of Anesthesiology and Critical Care, Paris, France. F. Revaux, AP-HP, Henri Mondor Hospital, Emergency Medical Services (SAMU) 94, Creteil, France. J. D. Ricard, AP-HP, Louis Mourier Hospital, Intensive Care Unit, Colombes, France. C. Richard, AP-HP, Bicetre Hospital, Medical Intensive Care Unit, Le Kremlin-Bicetre, France. B. Riou, AP-HP, Pitie-Salpetriere Hospital, Sorbonne University (Pierre et Marie Curie University – Paris 6), Department of Emergency Medicine and Surgery, Paris, France. F. Roussin, AP-HP, Saint Louis Hospital, Department of Anaesthesia and Surgical Intensive Care Medicine, Paris, France. F. Santoli, Robert Ballanger Hospital, Intensive Care Unit, Aulnay-sous-Bois, France. F. Schortgen, Centre Hospitalier Intercommunal Créteil, Intensive Care Unit, Creteil, France. A. Sharifzadehgan, AP-HP, Georges Pompidou European Hospital, Department of Cardiology, Paris, France. T. Sharshar, AP-HP, Sainte Anne Hospital, Intensive Care Unit, Paris, France. G. Sideris, AP-HP, Sorbonne Paris Cite University (Paris Diderot University), Lariboisiere Hospital, Department of Cardiology, Paris, France. T. Similowski, AP-HP,Pitie-Salpetriere Hospital, Medical Intensive Care Unit and Respiratory Division, France. C. Spaulding, AP-HP, Georges Pompidou European Hospital, Department of Cardiology, Paris, France. J. L. Teboul, AP-HP, Bicetre Hospital, Medical Intensive Care Unit, Le Kremlin-Bicetre, France. J. F. Timsit, AP-HP, Bichat Hospital, Medical Intensive Care Unit, Paris, France. J. P. Tourtier, Brigade de Sapeurs Pompiers de Paris (BSPP), Paris, France. P. Tuppin, French National Health Insurance (CNAMTS), Paris, France. Ursat C, AP-HP, Raymond Poincare Hospital, Emergency Medical Services (SAMU) 92, Garches, France. O. Varenne, AP-HP, Cochin Hospital, Department of Cardiology, Paris, France. A. Vieillard-Baron, AP-HP, Ambroise Pare Hospital, Intensive Care Unit, Boulogne-Billancourt, France. S. Voicu, AP-HP, Lariboisiere Hospital, Intensive Care Unit, Paris, France. K. Wahbi, AP-HP, Cochin Hospital, Department of Cardiology, Paris, France. V. Waldmann, AP-HP, Georges Pompidou European Hospital, Department of Cardiology, Paris, France

Author contributions
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References

1. Narayan SM, Wang PJ, Daubert JP (2019) New concepts in sudden cardiac arrest to address an intractable epidemic: JACC state-of-the-art review. J Am Coll Cardiol 73:70–88
2. Debaty G, Labarere J, Frascone RJ, Wayne MA, Swor RA, Mahoney BD, Domeier RM, Olinger ML, O'Neil BJ, Yannopoulos D, Aufderheide TP, Lurie

KG (2017) Long-term prognostic value of gasping during out-of-hospital cardiac arrest. J Am Coll Cardiol 70:1467–1476
3. Bougouin W, Lamhaut L, Marijon E, Jost D, Dumas F, Deye N, Beganton F, Empana J-P, Chazelle E, Cariou A, Jouven X (2014) Characteristics and prognosis of sudden cardiac death in Greater Paris: population-based approach from the Paris Sudden Death Expertise Center (Paris-SDEC). Intensive Care Med 40:846–854
4. Lemiale V, Dumas F, Mongardon N, Giovanetti O, Charpentier J, Chiche J-D, Carli P, Mira J-P, Nolan J, Cariou A (2013) Intensive care unit mortality after cardiac arrest: the relative contribution of shock and brain injury in a large cohort. Intensive Care Med 39:1972–1980
5. Laver S, Farrow C, Turner D, Nolan J (2004) Mode of death after admission to an intensive care unit following cardiac arrest. Intensive Care Med 30:2126–2128
6. Witten L, Gardner R, Holmberg MJ, Wiberg S, Moskowitz A, Mehta S, Grossestreuer AV, Yankama T, Donnino MW, Berg KM (2019) Reasons for death in patients successfully resuscitated from out-of-hospital and in-hospital cardiac arrest. Resuscitation 136:93–99
7. Nolan JP, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, Genbrugge C, Haywood K, Lilja G, Moulaert VRM, Nikolaou N, Mariero Olasveengen T, Skrifvars MB, Taccone F, Soar J (2021) European resuscitation council and European society of intensive care medicine guidelines 2021: post-resuscitation care. Resuscitation 161:220–269
8. Berg Katherine M, Soar J, Andersen LW, Böttiger BW, Cacciola S, Callaway CW, Couper K, Cronberg T, D'Arrigo S, Deakin CD, Donnino MW, Drennan IR, Granfeldt A, Hoedemaekers CWE, Holmberg MJ, Hsu CH, Kamps M, Musiol S, Nation KJ, Neumar RW, Nicholson T, O'Neil BJ, Otto Q, de Paiva EF, Parr MJA, Reynolds JC, Sandroni C, Scholefield BR, Skrifvars MB, Wang TL et al (2020) Adult advanced life support: 2020 international consensus on cardiopulmonary resuscitation and emergency cardiovascular care science with treatment recommendations. Circulation 142:S92–S139
9. Panchal AR, Bartos JA, Cabañas JG, Donnino MW, Drennan IR, Hirsch KG, Kudenchuk PJ, Kurz MC, Lavonas EJ, Morley PT, O'Neil BJ, Peberdy MA, Rittenberger JC, Rodriguez AJ, Sawyer KN, Berg KM, Arafeh J, Benoit JL, Chase M, Fernandez A, de Paiva EF, Fischberg BL, Flores GE, Fromm P, Gazmuri R, Gibson BC, Hoadley T, Hsu CH, Issa M, Kessler A et al (2020) Part 3: adult basic and advanced life support: 2020 american heart association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 142:S366–S468
10. Callaway CW, Donnino MW, Fink EL, Geocadin RG, Golan E, Kern KB, Leary M, Meurer WJ, Peberdy MA, Thompson TM, Zimmerman JL (2015) Part 8: post-cardiac arrest care: 2015 American Heart Association guidelines update for cardiopulmonary resuscitation and emergency cardiovascular care. Circulation 132:S465-482
11. van Diepen S, Katz JN, Albert NM, Henry TD, Jacobs AK, Kapur NK, Kilic A, Menon V, Ohman EM, Sweitzer NK, Thiele H, Washam JB, Cohen MG (2017) Contemporary management of cardiogenic shock: a scientific statement from the American Heart Association. Circulation 136:e232–e268
12. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J, CAT Study investigators (2008) A comparison of epinephrine and norepinephrine in critically ill patients. Intensive Care Med 34:2226–2234
13. Annane D, Vignon P, Renault A, Bollaert P-E, Charpentier C, Martin C, Troché G, Ricard J-D, Nitenberg G, Papazian L, Azoulay E, Bellissant E, CATS Study Group (2007) Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. Lancet Lond Engl 370:676–684
14. Levy B, Bollaert PE, Charpentier C, Nace L, Audibert G, Bauer P, Nabet P, Larcan A (1997) Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. Intensive Care Med 23:282–287
15. Levy B, Clere-Jehl R, Legras A, Morichau-Beauchant T, Leone M, Frederique G, Quenot J-P, Kimmoun A, Cariou A, Lassus J, Harjola V-P, Meziani F, Louis G, Rossignol P, Duarte K, Girerd N, Mebazaa A, Vignon P, Mattei M, Thivilier C, Perez P, Auchet T, Fritz C, Boisrame-Helme J, Mercier E, Garot D, Perny J, Gette S, Hammad E, Vigne C et al (2018) Epinephrine versus norepinephrine for cardiogenic shock after acute myocardial infarction. J Am Coll Cardiol 72:173–182
16. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP (2007) Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. BMJ 335:806–808
17. Maupain C, Bougouin W, Lamhaut L, Deye N, Diehl J-L, Geri G, Perier M-C, Beganton F, Marijon E, Jouven X, Cariou A, Dumas F (2016) The CAHP (Cardiac Arrest Hospital Prognosis) score: a tool for risk stratification after out-of-hospital cardiac arrest. Eur Heart J 37:3222–3228
18. Bougouin W, Dumas F, Karam N, Maupain C, Marijon E, Lamhaut L, Jost D, Geri G, Beganton F, Varenne O, Spaulding C, Jouven X, Cariou A, Sudden Death Expertise Center (2018) Should we perform an immediate coronary angiogram in all patients after cardiac arrest? Insights from a Large French Registry. JACC Cardiovasc Interv 11:249–256
19. Waldmann V, Bougouin W, Karam N, Narayanan K, Sharifzadehgan A, Spaulding C, Varenne O, Cariou A, Jouven X, Marijon E, Paris-Sudden Death Expertise Center (Paris-SDEC) Investigators (2018) Coronary vasospasm-related sudden cardiac arrest in the community. J Am Coll Cardiol 72:814–815
20. Bougouin W, Dumas F, Lamhaut L, Marijon E, Carli P, Combes A, Pirracchio R, Aissaoui N, Karam N, Deye N, Sideris G, Beganton F, Jost D, Cariou A, Jouven X, Adnet F, Agostinucci JM, Aissaoui-Balanant N, Algalarrondo V, Alla F, Alonso C, Amara W, Annane D, Antoine C, Aubry P, Azoulay E, Beganton F, Benhamou D, Billon C, the Sudden Death Expertise Center investigators et al (2020) Extracorporeal cardiopulmonary resuscitation in out-of-hospital cardiac arrest: a registry study. Eur Heart J 41:1961–1971
21. Geri G, Guillemet L, Dumas F, Charpentier J, Antona M, Lemiale V, Bougouin W, Lamhaut L, Mira J-P, Vinsonneau C, Cariou A (2015) Acute kidney injury after out-of-hospital cardiac arrest: risk factors and prognosis in a large cohort. Intensive Care Med 41:1273–1280
22. Fishman GI, Chugh SS, Dimarco JP, Albert CM, Anderson ME, Bonow RO, Buxton AE, Chen P-S, Estes M, Jouven X, Kwong R, Lathrop DA, Mascette AM, Nerbonne JM, O'Rourke B, Page RL, Roden DM, Rosenbaum DS, Sotoodehnia N, Trayanova NA, Zheng Z-J (2010) Sudden cardiac death prediction and prevention: report from a National Heart, Lung, and Blood Institute and Heart Rhythm Society Workshop. Circulation 122:2335–2348
23. Jennett B, Bond M (1975) Assessment of outcome after severe brain damage. Lancet 1:480–484
24. Bascom KE, Dziodzio J, Vasaiwala S, Mooney M, Patel N, McPherson J, McMullan P, Unger B, Nielsen N, Friberg H, Riker RR, Kern KB, Duarte CW, Seder DB, International Cardiac Arrest Registry (INTCAR) (2018) Derivation and validation of the CREST model for very early prediction of circulatory etiology death in patients without ST-segment-elevation myocardial infarction after cardiac arrest. Circulation 137:273–282
25. Perkins GD, Jacobs IG, Nadkarni VM, Berg RA, Bhanji F, Biarent D, Bossaert LL, Brett SJ, Chamberlain D, de Caen AR, Deakin CD, Finn JC, Gräsner J-T, Hazinski MF, Iwami T, Koster RW, Lim SH, Huei-Ming MM, McNally BF, Morley PT, Morrison LJ, Monsieurs KG, Montgomery W, Nichol G, Okada K, Eng Hock Ong M, Travers AH, Nolan JP, Utstein Collaborators (2015) Cardiac arrest and cardiopulmonary resuscitation outcome reports: update of the Utstein Resuscitation Registry Templates for Out-of-Hospital Cardiac Arrest: a statement for healthcare professionals from a task force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia); and the American Heart Association Emergency Cardiovascular Care Committee and the Council on Cardiopulmonary, Critical Care, Perioperative and Resuscitation. Circulation 132:1286–1300
26. Chen Y-S, Lin J-W, Yu H-Y, Ko W-J, Jerng J-S, Chang W-T, Chen W-J, Huang S-C, Chi N-H, Wang C-H, Chen L-C, Tsai P-R, Wang S-S, Hwang J-J, Lin F-Y (2008) Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. Lancet Lond Engl 372:554–561
27. Sasson C, Rogers MAM, Dahl J, Kellermann AL (2010) Predictors of survival from out-of-hospital cardiac arrest: a systematic review and meta-analysis. Circ Cardiovasc Qual Outcomes 3:63–81
28. Rab T, Kern KB, Tamis-Holland JE, Henry TD, McDaniel M, Dickert NW, Cigarroa JE, Keadey M, Ramee S, Interventional Council, American College of Cardiology (2015) Cardiac arrest: a treatment algorithm for

emergent invasive cardiac procedures in the resuscitated comatose patient. J Am Coll Cardiol 66:62–73
29. Callaway CW (2013) Epinephrine for cardiac arrest. Curr Opin Cardiol 28:36–42
30. Tang W, Weil MH, Sun S, Noc M, Yang L, Gazmuri RJ (1995) Epinephrine increases the severity of postresuscitation myocardial dysfunction. Circulation 92:3089–3093
31. Ditchey RV, Lindenfeld J (1988) Failure of epinephrine to improve the balance between myocardial oxygen supply and demand during closed-chest resuscitation in dogs. Circulation 78:382–389
32. Dumas F, Bougouin W, Geri G, Lamhaut L, Rosencher J, Pène F, Chiche J-D, Varenne O, Carli P, Jouven X, Mira J-P, Spaulding C, Cariou A (2016) Emergency PCI in post-cardiac arrest patients without ST-segment elevation pattern: insights from the PROCAT II registry. JACC Cardiovasc Interv. https://doi.org/10.1016/j.jcin.2016.02.001
33. Negovsky VA (1972) The second step in resuscitation–the treatment of the 'post-resuscitation disease.' Resuscitation 1:1–7
34. Negovsky VA (1988) Postresuscitation disease. Crit Care Med 16:942–946
35. Jozwiak M, Bougouin W, Geri G, Grimaldi D, Cariou A (2020) Post-resuscitation shock: recent advances in pathophysiology and treatment. Ann Intensive Care 10:170
36. Laurent I, Monchi M, Chiche JD, Joly LM, Spaulding C, Cariou A, Rozenberg A, Carli P, Weber S, Dhainaut JF, others (2002) Reversible myocardial dysfunction in survivors of out-of-hospital cardiac arrest. J Am Coll Cardiol 40:2110–2116
37. Kern KB, Hilwig RW, Rhee KH, Berg RA (1996) Myocardial dysfunction after resuscitation from cardiac arrest: an example of global myocardial stunning. J Am Coll Cardiol 28:232–240
38. Adrie C, Adib-Conquy M, Laurent I, Monchi M, Vinsonneau C, Fitting C, Fraisse F, Dinh-Xuan AT, Carli P, Spaulding C, Dhainaut J-F, Cavaillon J-M (2002) Successful cardiopulmonary resuscitation after cardiac arrest as a 'sepsis-like' syndrome. Circulation 106:562–568
39. Levy B, Perez P, Perny J, Thivilier C, Gerard A (2011) Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. Crit Care Med 39:450–455
40. Ameloot K, De Deyne C, Eertmans W, Ferdinande B, Dupont M, Palmers P-J, Petit T, Nuyens P, Maeremans J, Vundelinckx J, Vanhaverbeke M, Belmans A, Peeters R, Demaerel P, Lemmens R, Dens J, Janssens S (2019) Early goal-directed haemodynamic optimization of cerebral oxygenation in comatose survivors after cardiac arrest: the Neuroprotect post-cardiac arrest trial. Eur Heart J 40:1804–1814
41. Jakkula P, Pettilä V, Skrifvars MB, Hästbacka J, Loisa P, Tiainen M, Wilkman E, Toppila J, Koskue T, Bendel S, Birkelund T, Laru-Sompa R, Valkonen M, Reinikainen M (2018) Targeting low-normal or high-normal mean arterial pressure after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med 44:2091–2101
42. Ameloot K, Jakkula P, Hästbacka J, Reinikainen M, Pettilä V, Loisa P, Tiainen M, Bendel S, Birkelund T, Belmans A, Palmers P-J, Bogaerts E, Lemmens R, De Deyne C, Ferdinande B, Dupont M, Janssens S, Dens J, Skrifvars MB (2020) Optimum blood pressure in patients with shock after acute myocardial infarction and cardiac arrest. J Am Coll Cardiol 76:812–824
43. Coopersmith CM, De Backer D, Deutschman CS, Ferrer R, Lat I, Machado FR, Martin GS, Martin-Loeches I, Nunnally ME, Antonelli M, Evans LE, Hellman J, Jog S, Kesecioglu J, Levy MM, Rhodes A (2018) Surviving sepsis campaign: research priorities for sepsis and septic shock. Intensive Care Med 44:1400–1426
44. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, Kumar A, Sevransky JE, Sprung CL, Nunnally ME, Rochwerg B, Rubenfeld GD, Angus DC, Annane D, Beale RJ, Bellinghan GJ, Bernard GR, Chiche J-D, Coopersmith C, De Backer DP, French CJ, Fujishima S, Gerlach H, Hidalgo JL, Hollenberg SM, Jones AE, Karnad DR, Kleinpell RM, Koh Y, Lisboa TC et al (2017) Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med 43:304–377
45. Laurikkala J, Wilkman E, Pettilä V, Kurola J, Reinikainen M, Hoppu S, Ala-Kokko T, Tallgren M, Tiainen M, Vaahersalo J, Varpula T, Skrifvars MB (2016) Mean arterial pressure and vasopressor load after out-of-hospital cardiac arrest: associations with one-year neurologic outcome. Resuscitation 105:116–122