

Epinephrine Versus Norepinephrine for Cardiogenic Shock After Acute Myocardial Infarction



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ABSTRACT

BACKGROUND Vasopressor agents could have certain specific effects in patients with cardiogenic shock (CS) after myocardial infarction, which may influence outcome. Although norepinephrine and epinephrine are currently the most commonly used agents, no randomized trial has compared their effects, and intervention data are lacking.

OBJECTIVES The goal of this paper was to compare in a prospective, double-blind, multicenter, randomized study, the efficacy and safety of epinephrine and norepinephrine in patients with CS after acute myocardial infarction.

METHODS The primary efficacy outcome was cardiac index evolution, and the primary safety outcome was the occurrence of refractory CS. Refractory CS was defined as CS with sustained hypotension, end-organ hypoperfusion and hyperlactatemia, and high inotrope and vasopressor doses.

RESULTS Fifty-seven patients were randomized into 2 study arms, epinephrine and norepinephrine. For the primary efficacy endpoint, cardiac index evolution was similar between the 2 groups ($p = 0.43$) from baseline (H0) to H72. For the main safety endpoint, the observed higher incidence of refractory shock in the epinephrine group (10 of 27 [37%] vs. norepinephrine 2 of 30 [7%]; $p = 0.008$) led to early termination of the study. Heart rate increased significantly with epinephrine from H2 to H24 while remaining unchanged with norepinephrine ($p < 0.0001$). Several metabolic changes were unfavorable to epinephrine compared with norepinephrine, including an increase in cardiac double product ($p = 0.0002$) and lactic acidosis from H2 to H24 ($p < 0.0001$).

CONCLUSIONS In patients with CS secondary to acute myocardial infarction, the use of epinephrine compared with norepinephrine was associated with similar effects on arterial pressure and cardiac index and a higher incidence of refractory shock. (Study Comparing the Efficacy and Tolerability of Epinephrine and Norepinephrine in Cardiogenic Shock [OptimaCC]; [NCT01367743](https://clinicaltrials.gov/ct2/show/study/NCT01367743)) (J Am Coll Cardiol 2018;72:173–82) © 2018 by the American College of Cardiology Foundation.



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**ABBREVIATIONS
AND ACRONYMS****AMI** = acute myocardial infarction**CS** = cardiogenic shock**ECLS** = extracorporeal life support**ICU** = intensive care unit**MAP** = mean arterial pressure**PCI** = percutaneous coronary intervention**PCO₂** = partial pressure of carbon dioxide**RCT** = randomized controlled trial**SAP** = systolic arterial pressure**SOFA** = Sequential Organ Failure Assessment**SVO₂** = venous oxygen saturation

Mortality among patients with cardiogenic shock (CS) complicating acute myocardial infarction (AMI) remains high even in patients undergoing early revascularization (1). Vasopressor agents are administered in almost 90% of patients with CS with a positive class II recommendation and Level of Evidence C in U.S. and European guidelines (2,3). The use of vasopressor agents during severe CS is justified by the fact that for many patients, the adequacy of end-organ blood flow is roughly correlated with blood pressure, with low blood pressures being associated with an increased risk of mortality (4). However, these recommendations are mostly based on experts' opinion due to the lack of randomized controlled trials (RCTs) comparing the effects of vasopressor agents in patients with CS (5-7). In a randomized

study comparing dopamine and norepinephrine (8), a subgroup analysis of 280 patients with CS found that dopamine was associated with increased 28-day mortality compared with norepinephrine, leading to a progressive decrease in dopamine use in this indication (9).

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Norepinephrine and epinephrine are currently the most commonly used vasopressor agents in clinical practice (4,9-12). Studies comparing epinephrine and norepinephrine in patients with septic shock found no significant differences in outcome (13). Nevertheless, these drugs may have certain specific effects in patients with CS that could influence outcome. Norepinephrine is likely less thermogenic than epinephrine and therefore may have a more desirable effect on myocardial oxygen consumption (14). During acute ischemic CS, norepinephrine induces favorable effects on myocardial function (15,16). Conversely, epinephrine may induce a higher cardiac index and deliver available nutrients very rapidly to the heart through lactate production (17). Two

retrospective studies further suggested that epinephrine may have deleterious effects associated with greater circulating cardiovascular biomarkers in patients with CS (10,18). Moreover, despite these potential negative warnings, epinephrine is still used to treat the most severe forms of CS after myocardial infarction. However, none of these findings has been assessed prospectively in this specific clinical setting. The recent scientific statement from the American Heart Association recommends performing RCTs to identify the optimal vasopressor regimen in these patients (19). In light of this information, the present prospective, double-blind, multicenter RCT was designed to compare both the hemodynamic efficacy and tolerance of epinephrine and norepinephrine in patients with CS secondary to percutaneous coronary intervention (PCI)-treated AMI.

METHODS

STUDY DESIGN AND OVERSIGHT. The University Hospital Center in Nancy (France) designed and sponsored this multicenter, double-blind randomized trial. Trial administration, data management, and statistical analysis were performed by the sponsor. The executive committee had unrestricted access to the data, and the authors analyzed the data and prepared the manuscript.

This multicenter RCT was conducted between September 2011 and August 2016 in 9 French intensive care units (ICUs). The trial was registered in June 2011 before inclusion of the first patient. The last center was opened in June 2013. Secondary outcome measures and the statistical analysis plan were updated on April 19, 2017, before freezing of the database (April 24, 2017). The study received the approval of the Nancy Hospital Institutional Review Board. Written informed consent was obtained from the patients or their closest relatives. The trial was overseen by an independent data safety monitoring board.

STUDY POPULATION. Patients were eligible if they were >18 years of age and fulfilled the following criteria: 1) CS due to AMI successfully revascularized

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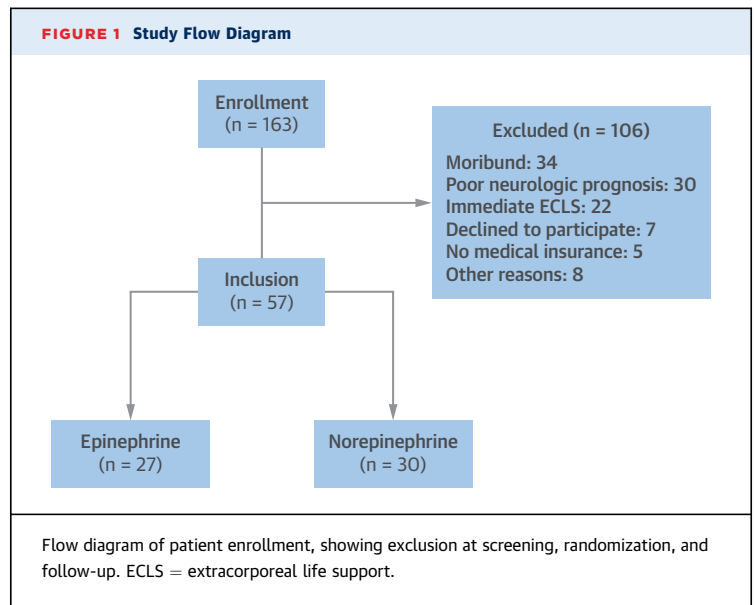
by using PCI; 2) systolic arterial pressure <90 mm Hg or mean arterial pressure (MAP) <65 mm Hg without a vasopressor agent or need for vasopressor therapy to correct hypotension; 3) cardiac index <2.2 l/min/m² in the absence of vasopressor or inotrope therapy; 4) pulmonary artery occlusion pressure >15 mm Hg or echocardiographic evidence of high pressure; 5) echocardiographic ejection fraction <40% without inotrope support (this criterion was not taken into account in instances of treatment with dopamine, norepinephrine, epinephrine, dobutamine, or milrinone); 6) at least one evidence of tissue hypoperfusion (e.g., skin mottling, oliguria, elevated lactate level, altered consciousness); and 7) an inserted pulmonary artery catheter. In patients already undergoing vasopressor therapy before randomization, the study drug had to be introduced no more than 6 h after the start of the open-label vasopressor treatment.

Exclusion criteria were shock of other origin; immediate indication for extracorporeal life support (ECLS); patient age <18 years; cardiac arrest with early signs of cerebral anoxia; septic, toxic, and obstructive cardiomyopathy; patient without medical insurance; adult patient under legal protection; and patients considered moribund by the attending physician. Moribund status was defined according to a state of imminent death with no medical therapeutic option.

RANDOMIZATION AND BLINDING. Randomization was computer generated, based on random blocks of 4, and stratified according to participating ICU. Treatment assignments and patient reference number were placed in sealed, opaque envelopes, which were opened by an independent pharmacist in charge of the preparation of the study drugs. Norepinephrine or epinephrine syringes were prepared extemporaneously by the pharmacist. Each syringe was subsequently labeled with the patient's number only and was indistinguishable. Physicians, nurses, and the local research staff were unaware of treatment assignments.

STUDY TREATMENTS AND PROTOCOL. Vasopressor doses are expressed in micrograms per kilogram per minute. Doses were increased by 0.02 µg/kg/min (or higher in emergency cases). The targeted MAP was 65 to 70 mm Hg (16). At inclusion (hour [H] 0), the blind syringe was added to the open-label vasopressor agent and as soon as MAP increased, the nurses in charge decreased and subsequently discontinued administration of the open-label vasopressor agent.

A patient was considered to be weaned from vasopressor therapy after 24 h of hemodynamic



stability without vasopressor support. During this time lag, if MAP decreased to <65 to 70 mm Hg, the study drug was reintroduced. Thereafter, an open-label vasopressor agent was used if clinically necessary. The study period lasted a maximum of 60 days. In case of failure to reach a MAP of 65 to 70 mm Hg or in case of arrhythmias refractory to therapy during treatment with the study drug, the attending physician could switch to open-label vasopressor therapy. All other treatment decisions were left to the discretion of the attending physicians.

MEASURED VARIABLES. The following data were recorded at H0 (randomization), H2, H4, H6, H12, H24, H48, and H72: vital signs, systolic arterial pressure (SAP), diastolic arterial pressure, MAP, heart rate, right atrial pressure (RAP), systolic pulmonary artery pressure, diastolic pulmonary artery pressure, mean pulmonary artery pressure (mPAP), pulmonary artery occlusion pressure, mixed venous oxygen saturation (SVO₂), cardiac index, echocardiographic left ventricular ejection fraction, arterial and mixed-venous blood gases, arterial lactate, and doses of vasoactive agents (cumulated and maximal). Biological variables, microbiological data, and antibiotic therapy were recorded daily for the first 7 days and thereafter on days 14, 21, and 28.

Plasma samples were collected at H0, H24, H48, and H72; they were stored at the study sites at -20°C, followed by storage at -80°C at the central laboratory. Growth differential factor 15, plasma high-sensitivity troponin T levels, and N-terminal pro-B-type natriuretic peptide levels were measured.

TABLE 1 Baseline Characteristics of the Study Population

	Epinephrine (n = 27)	Norepinephrine (n = 30)	p Value
Age, yrs	68 (55-79)	66 (55-77)	0.63
Sex			0.047
Male	14 (52)	24 (80)	NA
Female	13 (48)	6 (20)	NA
Body mass index, kg/m ²	25.2 (22.3-27.4)	25.4 (22.0-27.6)	0.98
Heart rate, beats/min	100 (70-118)	88 (75-110)	0.36
Systolic AP, mm Hg	109 (93-125)	98 (95-116)	0.29
Diastolic AP, mm Hg	54 (44-61)	57 (51-65)	0.14
Mean AP, mm Hg	72 (69-79)	71 (66-83)	0.62
Medical history			
Hypertension	8 (30)	6 (20)	0.54
Diabetes	2 (7)	4 (13)	0.67
Stroke	2 (7)	2 (7)	0.99
Myocardial infarction	2 (7)	2 (7)	0.99
Resuscitation before inclusion	11 (41)	18 (60)	0.19
SAPS 2 score	59 (45-74)	54.5 (44-65)	0.46
SOFA score	10 (9-12)	9 (8-12)	0.32
Duration of shock before randomization, h	6.1 (4.5-8.0)	6.0 (4.6-8.0)	0.71
Vasopressor treatment before inclusion	NA	NA	0.43
Epinephrine	8 (30)	5 (17)	NA
Norepinephrine	19 (70)	24 (80)	NA
None	0 (0)	1 (3)	NA
ST-segment elevation	26 (96)	29 (97)	0.99
Arterial lactate, mmol/L	5.00 (2.70-6.06)	2.93 (1.94-4.82)	0.068
Mechanical ventilation	26 (96)	30 (100)	0.99
LVEF, %	34 (24-48)	34 (26-40)	0.65

Values are median (25th to 75th percentile) or n (%).
AP = arterial pressure; LVEF = left ventricular ejection fraction; NA = not applicable; SAPS = simplified acute physiology score; SOFA = Sequential Organ Failure Assessment.

CALCULATED VARIABLES. Cardiac index, oxygen delivery index, oxygen consumption index, systemic vascular resistance index, and stroke volume index were calculated by using standard formulae. The simplified acute physiology score 2 was calculated at the time of admission to the ICU and at the time of enrollment in the study; the Sequential Organ Failure Assessment (SOFA) score was calculated daily for the first 7 days and thereafter on days 14, 21, and 28.

OUTCOMES. Primary efficacy and safety endpoints. The change in cardiac index was the primary outcome variable. Cardiac index was measured at randomization (H0) and at H2, H4, H6, H12, H24, H48, and H72. The main safety endpoint was the incidence of refractory CS. Refractory CS was defined as CS with major cardiac dysfunction assessed according to echocardiography, elevated lactate level, and acute deterioration of organ function (e.g., oliguria, liver failure) despite the use of >1 µg/kg/min of epinephrine/norepinephrine or dobutamine >10 µg/kg/min and/or intra-aortic balloon support and sustained hypotension

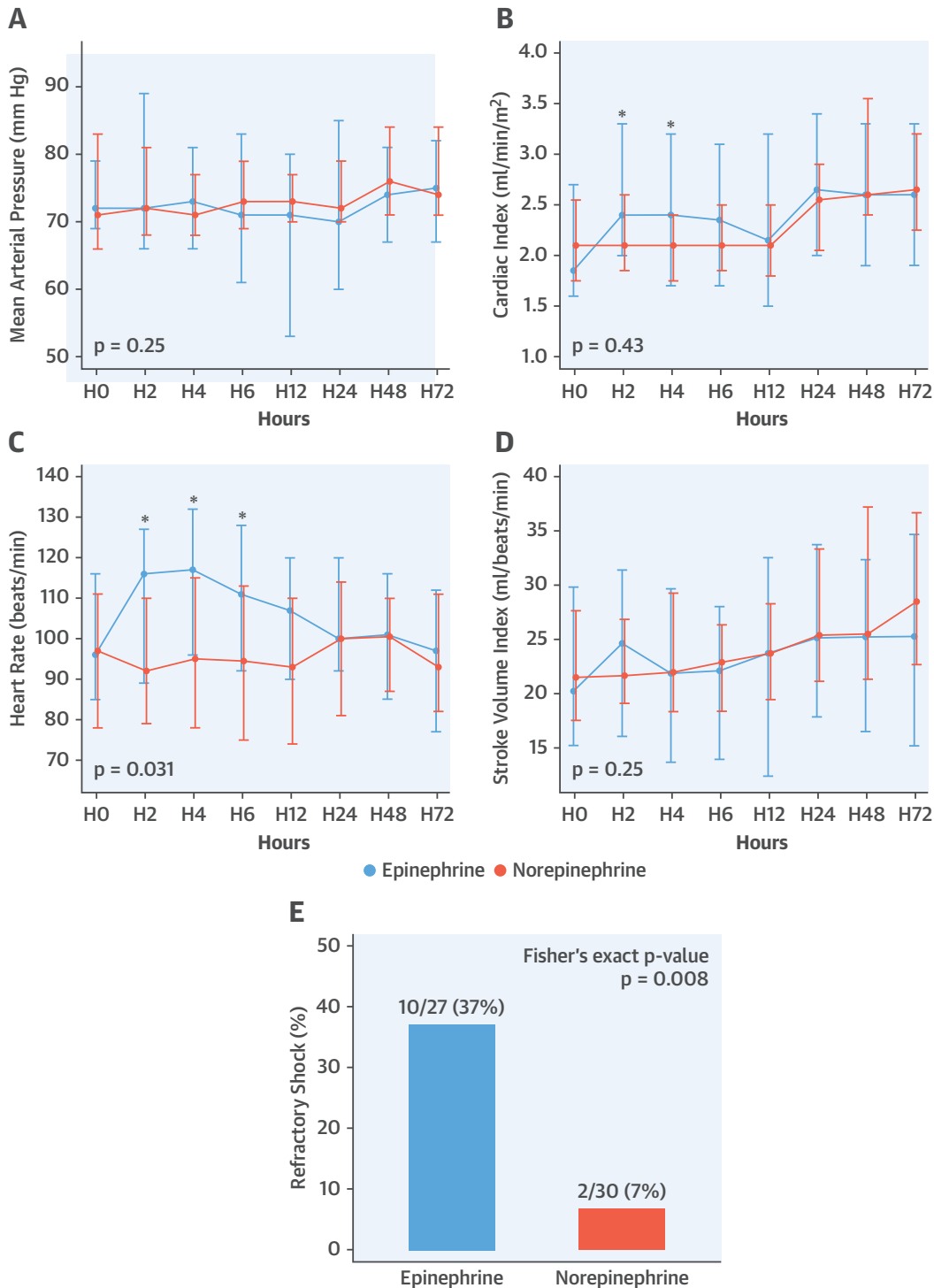
(SAP <90 mm Hg or MAP <65 mm Hg) despite adequate intravascular volume. This event was defined by the independent safety monitoring board at the first meeting (September 2015) while reviewing adverse events. The blind follow-up of the serious adverse event declared by the investigators to the pharmacovigilance team revealed an expected global mortality but a high incidence of refractory CS when considering the entire population. Because refractory CS was not an expected serious adverse event of both drugs, this event was not specifically followed. After having unblinding the cases, the data and safety monitoring board found an imbalance between the 2 groups for refractory CS incidence as declared by the investigators. Therefore, the pharmacovigilance team of the trial provided advice for the systematic reporting of this serious adverse event as a serious adverse event of interest and asked the main investigator to perform a review of these cases. This new safety event was reported to the ANSM (French Agency for Drugs Safety), which terminated the study in April 2016. At the end of the study but before freezing the database, all case report forms were reviewed by 2 physicians not participating in the study to both confirm the diagnosis of refractory shock and to search for other potential cases that were not declared.

Secondary efficacy and safety outcomes. Secondary efficacy endpoints were changes in other hemodynamic variables over time, cardiac power index (20), use of inotropes, lactate level and lactate clearance (21), biomarker levels, and SOFA score evolution during the first 72 h. Regarding safety, specifically screened adverse events comprised arrhythmias (i.e., ventricular tachycardia, ventricular fibrillation, atrial fibrillation).

STATISTICAL ANALYSIS. The analysis used an intention-to-treat strategy; patients were analyzed according to their randomization arm. The primary efficacy endpoint was the cardiac index. To detect a difference of at least 0.64 SDs between the 2 groups, a sample size of 40 patients per group was required to achieve 80% power with a 2-tailed significance level of 5%. Thus, according to the baseline cardiac index of SHOCK (Should We Emergently Revascularize Occluded Coronaries for Cardiogenic Shock?) trial patients (22), for an initial average cardiac index of 1.8 ± 0.6 l/min/m², a statistically significant result corresponded to a difference of 0.38 l/min/m².

All analyses were performed by using R statistical software (R Foundation for Statistical Computing, Vienna, Austria). The 2-tailed significance level was set at $p < 0.05$. Continuous variables are described as

CENTRAL ILLUSTRATION Epinephrine Versus Norepinephrine in Cardiogenic Shock After Acute Myocardial Infarction



Levy, B. et al. J Am Coll Cardiol. 2018;72(2):173-82.

(A) Mean arterial pressure; (B) cardiac index; (C) heart rate; (D) stroke volume index; and (E) refractory cardiogenic shock distribution.

TABLE 2 Serious Adverse Events and Outcomes

	Epinephrine (n = 27)	Norepinephrine (n = 30)	p Value*	Odds Ratio (95% Confidence Interval)	p Value†
Refractory shock	10 (37)	2 (7)	0.008	8.24 (1.61-42.18)	0.011
Arrhythmia	11 (41)	10 (33)	0.59	1.37 (0.47-4.05)	0.56
ECLS	3 (11)	1 (3)	0.34	3.62 (0.35-37.14)	0.28
Death	14 (52)	11 (37)	0.29	1.86 (0.65-5.36)	0.25
Death within 7 days	8 (30)	3 (10)	0.093	3.79 (0.89-16.17)	0.072
Death within 28 days	13 (48)	8 (27)	0.11	2.55 (0.84-7.72)	0.097

Values are n (%) unless otherwise indicated. Odds ratios were expressed by using the norepinephrine group as reference. *p value from the Fisher exact test. †p value from the Wald test.
ECLS = extracorporeal life support.

median (interquartile range) and categorical variables as frequencies (percentages). Comparison of baseline characteristics according to treatment group was conducted by using the nonparametric Wilcoxon test for continuous variables and the Fisher exact test for categorical variables. Associations between treatment group and adverse events were assessed by using logistic regression model. Odds ratios are presented with their 95% confidence intervals using the norepinephrine group as reference. Survival rates for the composite outcome of “death and/or ECLS implementation within 7 days” according to treatment group are illustrated by using Kaplan-Meier analyses. Differences between survival curves were analyzed by using the log-rank test.

The evolution of outcomes (MAP, cardiac index, heart rate, stroke volume index, arterial lactate, cardiac double product, cardiac power index, and SvO₂) during the hemodynamic assessment period (72 h) was compared in the 2 groups by using repeated-measures analysis of variance based on the ranks of the values with the rank of baseline value as adjustment covariate. Because the post-baseline values were constrained by the clinical events observed during the follow-up (death or ECLS implantation), each value was ranked from lowest to highest at each time point, with the worst rank attributed for deceased patients at each time point after their death and the second worst rank for patients who underwent ECLS at each time point after their implantation (additional details are provided in the [Online Appendix](#)). The evolution of other parameters was compared in the 2 groups by using repeated measures analysis of variance with baseline value as the adjustment covariate. It should be noted that certain outcomes were not specified a priori as primary/secondary efficacy or safety endpoints. Therefore, analysis of these outcomes must be considered as a post hoc analysis.

RESULTS

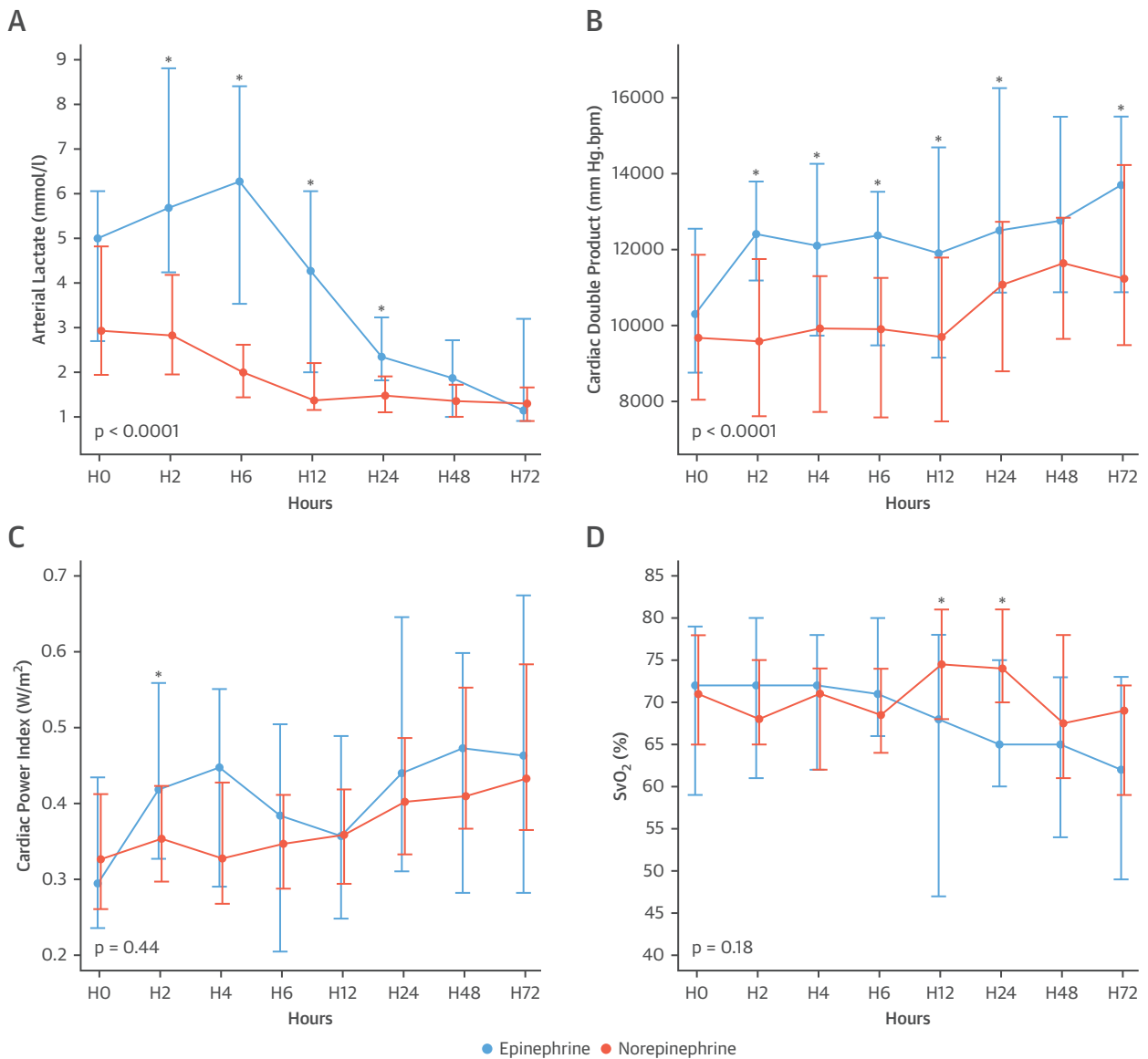
STUDY POPULATION. Among 163 screened patients, 106 were excluded predominantly for moribund status (n = 34), cardiac arrest with early signs of cerebral anoxia (n = 30), and early ECLS requirement (n = 22) ([Figure 1](#)). A total of 57 patients were ultimately included, 27 in the epinephrine group and 30 in the norepinephrine group. Patient characteristics at inclusion are provided in [Table 1](#) and [Online Table 1](#). With the exception of sex, there was no difference between the 2 groups. Eleven patients (41%) in the epinephrine group and 18 patients (60%) in the norepinephrine group were successfully resuscitated after a cardiac arrest before enrollment in the study (p = 0.19). At inclusion, 56 (98%) of 57 patients were mechanically ventilated. Coronary and PCI characteristics are described in [Online Table 2](#).

In all studied patients, urgent PCI revascularization was successfully performed with a resulting Thrombolysis In Myocardial Infarction flow grade score of 3 at the end of the procedure. The open-label vasopressor regimen before randomization did not differ between groups. An intra-aortic balloon pump was inserted after PCI in 16 (59%) of 27 patients in the epinephrine group and in 15 (50%) of 30 patients in the norepinephrine group (p = 0.60). No mechanical complication of AMI was encountered.

PRIMARY EFFICACY AND SAFETY OUTCOME. For the main efficacy endpoint, using an intention-to-treat analysis strategy and taking into account patients who died or underwent ECLS implantation as worst outcomes (as detailed in the Methods section), cardiac index evolution did not significantly differ between the epinephrine and norepinephrine groups (p = 0.43) ([Central Illustration](#)). Cardiac index was transiently higher in the epinephrine group at H2 (p = 0.011) and H4 (p = 0.036) ([Online Table 3](#)).

For the main safety endpoint, epinephrine was associated with a higher incidence of refractory CS (10 of 27 [37%] vs. 2 of 30 [7%]; p = 0.011) ([Central Illustration, Table 2](#)). Given the higher incidence of refractory shock in the epinephrine group, the data and safety monitoring board terminated the study prematurely. Importantly, this adverse event was not planned as the primary safety outcome at trial initiation. It was, however, systematically recorded as an outcome of interest and carefully reviewed after the vigilance team of the trial identified an unexpected high rate of this outcome during the first year of the study. As a consequence, although this event was not defined before trial initiation, it was nonetheless defined during the course of the trial.

FIGURE 2 Hemodynamic, Metabolic, and Cardioenergetic Parameters at Baseline (H0) and at H2, H4, H6, H12, H24, H48 and H72



(A) Arterial lactate; (B) cardiac double product; (C) cardiac power index; and (D) mixed venous oxygen saturation (SvO₂). All parameters and variables were compared between the 2 groups at baseline (hour [H] 0) and at H2, H4, H6, H12, H24, H48, and H72 with analysis of variance adjusted on baseline measurement. Data are presented as median (interquartile ranges). The p values were calculated by using repeated measures analysis of variance. *p < 0.05.

SECONDARY HEMODYNAMIC AND METABOLIC EFFICACY ENDPOINTS. Regarding the study drugs, the dose needed to obtain a MAP of 70 mm Hg was $0.7 \pm 0.5 \mu\text{g/kg/min}$ in the epinephrine group and $0.6 \pm 0.7 \mu\text{g/kg/min}$ in the norepinephrine group ($p = 0.66$). There was no statistically significant difference with regard to duration ($p = 0.15$), the dose at different time points (from H0 to H72; $p = 0.66$), and the maximal dose ($p = 0.79$) of study drugs in the 2 groups (Online Table 4). The evolution of SAP

($p = 0.11$), diastolic arterial pressure ($p = 0.13$), and MAP ($p = 0.80$) during the first 3 days of the study was similar between groups (Online Table 5).

Mean heart rate increased significantly in the epinephrine group, whereas it did not change significantly in the norepinephrine group ($p = 0.031$) (Central Illustration, Online Table 3). The evolution of stroke volume index ($p = 0.25$) and cardiac power index ($p = 0.064$) was similar between groups (Figure 2). Cardiac double product, a surrogate of

myocardial oxygen consumption, increased in the epinephrine group, whereas it did not change in the norepinephrine group. The venous-arterial partial pressure of carbon dioxide (PCO₂) gradient was similar between the epinephrine and norepinephrine groups ($p = 0.59$) (Online Table 5). The mean systemic vascular resistance index progressively decreased with no significant differences ($p = 0.44$). Mean pulmonary artery pressure ($p = 0.48$) and pulmonary artery occlusion pressure ($p = 0.38$) evolved similarly between the 2 groups. Finally, left ventricular ejection fraction progressively increased in a similar manner between both groups ($p = 0.87$).

Regarding the combined use of inotropes, dobutamine was used in 18 (67%) of 27 patients in the epinephrine group and in 20 (67%) of 30 patients in the norepinephrine group ($p = 0.99$). Mean dobutamine treatment duration was 22 (7 to 72) h in the epinephrine group and 90 (63 to 161) h in the norepinephrine group ($p = 0.0009$). There was no statistically significant difference in dobutamine at the different time points (from H0 to H72; $p = 0.78$) or in the maximal dose ($p = 0.88$) (Online Table 4).

Regarding metabolic changes, during the first 24 h, epinephrine use was associated with metabolic acidosis ($p = 0.0004$) and increased lactate level ($p < 0.0001$) (Figure 2), whereas arterial pH increased and lactate level decreased in the norepinephrine group. Lactate clearance was observed much earlier and occurred at a faster pace in the norepinephrine group ($p < 0.0001$). The evolution of SVO₂ ($p = 0.20$) (Online Table 3), oxygen consumption index ($p = 0.67$) and oxygen delivery index ($p = 0.69$) during the study period was similar between the 2 groups (Online Table 5).

Regarding organ dysfunction, the SOFA score and its components did not differ between the 2 groups, either at inclusion or during patient course ($p = 0.44$). There were no differences in variations during the study period with regard to creatinine, urea, diuresis, aspartate transaminase, and bilirubin levels between the 2 groups (Online Table 6). The decrease in alanine transaminase level occurred faster in the norepinephrine group ($p = 0.011$). Renal replacement therapy was used in 7 (26%) of 27 patients in the epinephrine group and in 2 (7%) of 30 patients in the norepinephrine group ($p = 0.07$). No statistically significant difference was observed in levels of the cardiac biomarkers N-terminal pro-B-type natriuretic peptide ($p = 0.20$) and cardiac troponin T ($p = 0.21$) during the first 72 h. By contrast, levels of the cardiovascular prognostic marker growth differential factor 15 were markedly higher in the epinephrine

versus norepinephrine group from H24 to H72 ($p = 0.002$) (Online Figure 1).

The incidence of arrhythmia was not significantly different between the epinephrine and norepinephrine groups (11 of 27 [41%] vs. 10 of 30 [33%]; $p = 0.56$). Two patients from the epinephrine group were switched to open-label norepinephrine due to sustained ventricular tachycardia.

MORTALITY. Death at 60 days occurred in 14 (52%) of 27 patients in the epinephrine group and in 11 (37%) of 30 patients in the norepinephrine group ($p = 0.25$) (Table 2). Epinephrine use was associated with a trend toward an increased risk of death on day 7 ($p = 0.08$) and with a significantly higher risk of death or ECLS requirement on day 7 ($p = 0.031$) (Online Figure 2). There was also a trend for an increased risk of death or ECLS requirement on day 28 ($p = 0.064$). Post hoc results including ECLS implantation are further described in Online Table 7.

DISCUSSION

This trial is the first randomized study to compare epinephrine and norepinephrine in patients with CS complicating AMI. The main result of the present study is that epinephrine use was associated with very transient improvement in cardiac index but with marked safety concerns, including refractory shock. Compared with norepinephrine, epinephrine administration was also associated with an increase in heart rate, prolonged acidosis, and lactatemia. Other hemodynamic variables did not differ significantly between treatment groups.

COMPARISON BETWEEN NOREPINEPHRINE AND EPINEPHRINE IN CARDIOGENIC SHOCK. The comparison of the 2 groups was conducted by using a statistical method that allowed inclusion of the data of the patients who died or underwent ECLS implantation. Briefly, because comparisons were based on ranks, death or ECLS implantation was considered as having a worst rank than largely abnormal values of continuous data in the absence of these events. This strategy maintained the intention-to-treat nature of the analysis. Both drugs were efficient in increasing MAP. As previously described (23), MAP was always higher than the target MAP with no differences between the 2 groups. Epinephrine was associated with a marked and sustained increase in heart rate compared with norepinephrine-treated patients. This outcome was likely due to the high number of beta₂-adrenoceptors present in the atria (approximately 30% of the total beta-adrenoceptors) (24,25).

The tachycardia observed in the epinephrine group led to a transient increase in cardiac index from H0 to H4, whereas stroke index was similar in both groups. Importantly, epinephrine-treated patients exhibited substantial lactic acidosis, an increased cardiac double product (which can be considered as a surrogate of myocardial oxygen consumption) (26), and similar perfusion markers such as SVO_2 and arteriovenous PCO_2 . Thus, it is highly likely that all of these effects were linked to receptor affinity differences because only epinephrine acts on β_2 -receptors (27). Experimentally, the main difference between the 2 drugs is that epinephrine increases the contractile force of myocardial fibers to a lesser degree than norepinephrine at the expense of a higher energy cost leading to lower cardiac efficiency (28). Moreover, when used at higher doses, epinephrine is associated with negative inotropic effects. We and others have shown that epinephrine-induced lactic acidosis is a cost-energy mechanism mainly related to the activation of the sarcolemmal sodium-potassium adenosine triphosphatase pump through β_2 -receptors and cAMP (cyclic adenosine monophosphate) production in an adenosine triphosphate-consuming process (29,30).

EPINEPHRINE USE AND REFRACTORY CARDIOGENIC SHOCK. Despite premature termination of the trial and the relatively small treatment groups, we were able to identify a clinically meaningful difference in the number with refractory CS with epinephrine use compared with norepinephrine. The main aim of resuscitation during CS is to improve global perfusion and not to obtain a predefined cardiac index. Monitoring tissue perfusion can be achieved by using arterial lactate, venoarterial gradients in PCO_2 , and central venous or mixed venous oxygen saturation (3,31). Thus, to obtain the same effect on global perfusion and tissue oxygenation, epinephrine-treated patients had higher cardiac double product, lactic acidosis, and a differential regulation of growth differential factor 15 pathway (a stress responsive cytokine that increases in response to hypoxia, oxidative stress, inflammation, and cell injury) (32). Overall, these effects could explain the increased occurrence of refractory CS in epinephrine-treated patients secondary to excessive adrenergic overstimulation likely mimicking an acute catecholamine-induced cardiomyopathy as previously described with epinephrine use (33) or upon administration of very high doses of dobutamine (34).

STUDY LIMITATIONS. The main limitation is that our study lasted 4 years and included only 57 patients

during this period. Two reasons may explain this low inclusion rate. First, at the time of the study, the concept of a cardiac center and heart team was not developed in France. Therefore, in the same hospital, a patient with CS secondary to myocardial infarction might have been treated in a different ICU, leading to a relatively low incidence of this pathology in 1 specific ICU. Second, the mandatory use of a pulmonary artery catheter at the time, which is currently rarely used in France for shock monitoring, markedly limited the number of potential centers involved in the study. Nevertheless, our studied population was similar to studies assessing the most severe presentations of CS related to AMI both for clinical characteristics and mortality (1,19,35,36). Finally, the increase in cardiac index and heart rate associated with lactic acidosis has been described with epinephrine use in both septic (37), hemorrhagic, and cardiogenic (38) shock. Nevertheless, because CS encompasses a wide spectrum of hemodynamic states (19), the potential deleterious effects associated with its use such as refractory CS may differ in CS due to other etiologies (e.g., poisoning, post-cardiopulmonary bypass, myocarditis).

CONCLUSIONS

In patients with CS secondary to acute MI, the use of epinephrine compared with norepinephrine was associated with similar effects on arterial pressure and cardiac index and a higher incidence of refractory shock.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL

SKILLS: In patients with AMI complicated by CS who have undergone successful primary angioplasty, shock is less refractory when arterial pressure is supported with norepinephrine rather than with epinephrine.

TRANSLATIONAL OUTLOOK: Future studies should compare the myocardial energetic effects of various catecholamines and their impact on clinical outcomes in patients with CS in clinical settings other than AMI.

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KEY WORDS acute myocardial infarction, cardiogenic shock, epinephrine, norepinephrine, vasopressor

APPENDIX For a supplemental statistical analysis section and list of trial collaborators, as well as supplemental figures and tables, please see the online version of this paper.