Anaesth Crit Care Pain Med 42 (2023) 101200

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Original Article

Epidemiology, risk factors and outcomes of norepinephrine use in cardiac surgery with cardiopulmonary bypass: a multicentric prospective study

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ARTICLE INFO

Article history:
Available online xxx

Keywords:
Norepinephrine
Vasopressor
Cardiac surgery
Cardiopulmonary bypass
Shock
Dobutamine
Sepsis
Acute kidney injury

ABSTRACT

Background: The present study was designed to describe the prevalence of norepinephrine use, the factors associated with its use, and the incidence of postoperative complications according to norepinephrine use, in patients undergoing cardiac surgery with cardiopulmonary bypass.
Method: We performed a prospective, multicenter, observational study in 4 University-affiliated medico-surgical cardiovascular units. We analyzed all patients treated with cardiac surgery after excluding pre-ECMO surgery, LVAD implantation, heart transplantation and intra-operative hemorrhage.
Results: Of 9316 patients screened during the study period, 2862 were included and 2510 were analyzed. Among them, 1549 (61%) were treated with norepinephrine with a median maximal dose of 0.11 [0.06–0.2] $\mu g.kg^{-1}.min^{-1}$ and a median duration of 10 h [2–24]. Norepinephrine was most often started in the operating room before cardiopulmonary bypass. The multiple regression logistic analysis identified several modifiable (haematocrit, maintenance of beta-blocker, cardiopulmonary bypass time, glucose-insulin-potassium, Custodiol cardioplegia, Delnido cardioplegia, and fibrinogen transfusion) and non-modifiable factors (age, ASA score, chronic high blood pressure, coronary disease, dyslipidemia, right ventricular dysfunction, left ventricular dysfunction, active endocarditis, and valvular aortic surgery) associated with norepinephrine use. Mortality, morbidity (neurological and renal complications, death) and length of stay in the ICU were higher in patients treated with norepinephrine.
Conclusion: Norepinephrine is often used in cardiac surgical patients but for <24 h with a low dose. Many preoperative and surgical factors are associated with norepinephrine use. Patients supported by norepinephrine have a higher incidence of major postoperative events.

Abbreviations: AKI, acute kidney injury; ECMO, extra-corporeal membrane oxygenation; LVEF, left ventricular ejection function; CS, post-cardiotomy shock.

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https://doi.org/10.1016/j.accpm.2023.101200

Introduction

Cardiac surgery is associated with hemodynamic disturbance with arterial hypotension in relation to low cardiac output syndrome and/or alteration in vasomotor tone [1,2]. Vasomotor tone alteration is usually assimilated to the vasoplegic syndrome that is treated with vasopressors [2]. The incidence of vasoplegic syndrome is wide depending on the definition used but remains a daily problem in cardiac surgery, since it is associated with an increase in length of stay in the intensive care unit, and hospitalization costs [2]. Studies have evaluated the epidemiology of vasoplegic syndrome but most of these studies are old, retrospective, single-centred with a low number of patients, and use different definitions of the vasoplegic syndrome [2–5]. In recent years, the concept of hemodynamic optimization of high-risk surgical patients evolved towards more active care to reduce complication risk. Thus, patients are more treated with vasopressors than in the past, to meet more stringent hemodynamic targets. A recent expert consensus has strongly recommended using norepinephrine (NE) as first-line vasopressor therapy in cardiac surgery [6]. NE use in cardiac surgery, the factors associated with its use, and the incidence of complications were not specifically studied yet. Most of the published studies have focused on vasoplegic syndrome or a comparison between catecholaminergic and non-catecholaminergic vasopressors [7–9].

Regarding the evolution of cardiac surgical technique, anaesthesia, and perioperative hemodynamic treatment, we hypothesized that NE may be the main and the most frequent vasopressor used in patients undergoing cardiac surgery with cardiopulmonary bypass. Patients supported with NE may represent a high-risk population with a high incidence of postoperative complications. In absence of data, we designed the present study to describe the prevalence of NE use, the factors associated with its use, and the incidence of complications in patients supported by NE.

Materials and methods

Study design

This was a multicenter observational prospective study approved by the French ethical committee (Comité De Protection Des Personnes Sud Mediterranee I, 2017-A01324-49, Chairman: Pr Y. JAMMES) for human subjects [10]. The study was conducted in the anesthesia and critical care cardiac surgical department of four university-affiliated tertiary hospitals from 2017 to 2021. All patients have received a written document for research purposes and gave their consent prior to participating. The study design adheres to the Medical Research Involving Human Subject Act requirements and the Declaration of Helsinki. The reporting of this study complied with STROBE guidelines.

Study population

The main inclusion criteria were as follows: patients aged $\geq$18 years who underwent cardiac surgery with the use of cardiopulmonary bypass (CPB). The main non-inclusion criteria were off-pump cardiac surgery, pre-operative VA-ECMO, left ventricular assist device, and heart transplantation. Other exclusion criteria were incomplete data (no missing data on variables assessed), and intra-operative hemorrhagic shock (intra-operative excessive bleeding that necessitates $\geq$ three units of red blood cell transfusion, or that delayed sternal closure [11]). For included patients, NE was noted when it was used in the operating room and/or in the intensive care unit (ICU).

Intraoperative and ICU management

Anesthesia, CPB procedures and post-operative management were left at the physicians' discretion, as previously described [12,13]. Circulatory support was guided to achieve predefined clinical endpoints: mean arterial pressure $\geq$ 65 mmHg, cardiac index $\geq$2.2 $L.min^{-1}.m^{-2}$ and urine output $\geq$0.5 $mL^{-1}.kg^{-1}.h^{-1}$. Electrocardiogram, pulse oxygen saturation and central venous blood pressure were continuously monitored. Scheduled blood tests included arterial/venous blood gas measurements on admission at ICU, and then several times a day on request by the attending physician. Once hemodynamic stability and normothermia were obtained and blood loss was considered acceptable ($<$1 $mL^{-1}.kg^{-1}.h^{-1}$), respiratory weaning was attempted. All patients were managed by a specialized team trained in post-operative cardiac surgery care.

Data collection

All data were anonymously, consecutively and prospectively recorded using a dedicated, secure, web-based system case report form (Ennov clinical software). The following variables were recorded: age, gender, body weight, height, personal medical history, personal medications, ASA score, EuroSCORE 2, preoperative left ventricular ejection fraction, right ventricular dysfunction, pulmonary artery pressure, emergency, redo surgery, number of procedure, type of surgery, type of cardioplegia, hypothermia (defined as the core temperature below 35°C), amount of intraoperative fluid, duration of anesthesia, duration of CPB, duration of aortic clamping, the need for intraoperative blood transfusion, acid tranexamic/aprotinin use, opioid/non-opioid anesthesia, dobutamine (duration, maximum posology), epinephrine (duration, maximum posology), creatinine value, time to extubation (hours), any occurrence of complications during the stay in the ICU or the hospital, and the length of stay (LOS) in the ICU and the hospital.

Endpoints and definition of complications

The primary endpoint was the number of patients treated with *tartrate norepinephrine* out of the context of intra-operative haemorrhagic shock. The maximal dose (in $\mu g.kg^{-1}.min^{-1}$) used in the operative room and ICU was noted. The duration time was defined as the total time treated with NE from the start of surgery to the end of ICU stays, expressed in hours.

The secondary endpoints were major adverse post-operative events (stroke, delirium, new onset of atrial fibrillation or flutter, low cardiac output syndrome, acute kidney injury (AKI), sepsis, and in-hospital death), total intraoperative fluids administered (ml), total propofol dose ($mg.kg^{-1}$), opioid use, vasopressor use (number of patients and higher dose), inotrope use (number of patients and higher dose), and total ICU/hospital LOS (in days). Complications were prospectively noted during the ICU and hospital stays. Complications were defined according to the European Perioperative Clinical Outcome definitions: neurological, cardiovascular, acute kidney injury, hemorrhagic, and infectious complications [12,14]. Stroke was defined as an embolic, thrombotic, or hemorrhagic cerebral event with persistent residual motor, sensory, or cognitive dysfunction (*e.g.*, hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed by brain computed tomography scan. Delirium was assessed using the Confusion Assessment Method for the Intensive Care Unit. AKI was defined according to kidney disease improving global outcomes (KDIGO) criteria. AKI stage 1 is defined as an increase in serum creatinine (SCr) by $\geq$0.3 $mg.dL^{-1}$ or an increase in SCr to $\geq$1.5

times baseline, or urine output < 0.5 mL.kg^{-1}.h^{-1} for 6–12 h. AKI stage 2 is defined as an increase in SCr to $\geq$2.0–2.9 times the baseline, or urine output < 0.5 mL.kg^{-1}.h^{-1} for $\geq$12 h. AKI stage 3 is defined as an SCR of up to 3.0 times the baseline or SCR increased to $\geq$4.0 mg.dL^{-1} or the initiation of renal replacement therapy or urine output $<$0.3 mL.kg^{-1}.h^{-1} for $\geq$24 h or anuria for $\geq$12 h.

To study the association between NE exposure and complications, a composite of post-operative Major Adverse Kidney and Cerebral Events was constructed. The composite score includes stroke, AKI, and death.

Statistical analysis

The trial was designed to describe the use of NE in cardiac surgery with cardiopulmonary bypass and to investigate the factors associated with its use. According to the literature and guidelines that consider one analysed factor per 10 events, it was decided to include 20 events per analysed factor to obtain a stable model. Thus, it will be possible to include up to 70 factors with a sample size of 2500 patients to analyse the risk factor of NE use. Taking into account the exclusion criteria, the sample size was increased to 3000 patients.

Normality was visually assessed using histograms and interquartile plots. Accordingly, quantitative data are presented as medians [interquartile range], and qualitative data are presented as frequencies and percentages.

A multivariate logistic regression model with a backward process (variables with a *p*-value of 0.20 were included) was performed. To take into account the effect of the centre, the centre was included in the multivariate logistic regression model. The association between risk factors and NE was evaluated by the odds

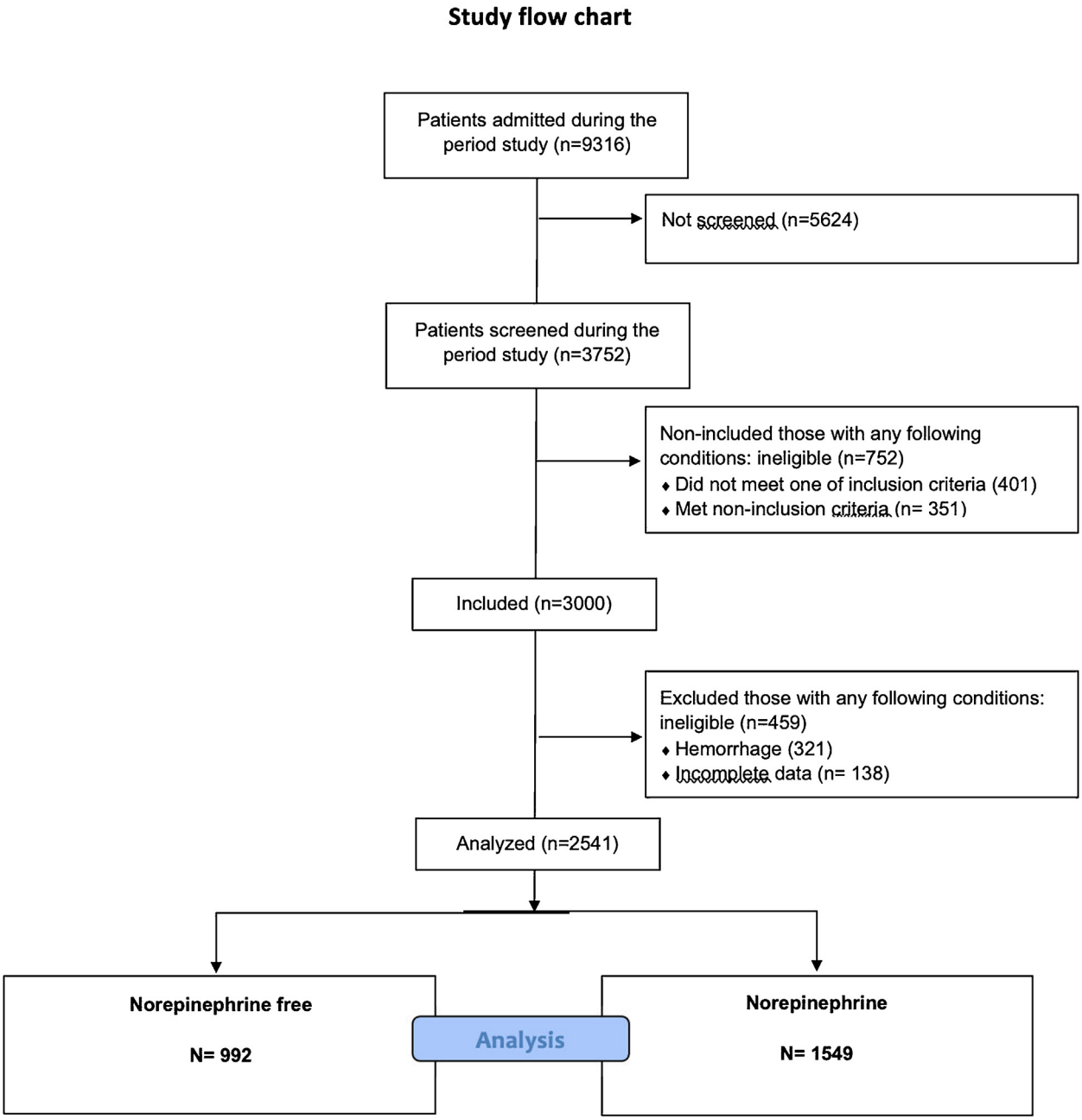

Fig. 1. Flow chart diagram of the study.

ratio (OR) and its [95% confidence interval]. Calibration of the final logistic model was assessed using the Hosmer–Lemeshow statistic.

We performed a propensity score matching to analyse the association between NE exposure and Major Adverse Renal and Cerebral Events. The propensity matching was performed as recommended [15], using a nearest-neighbour algorithm with 1:1 matching without replacement, and a calliper distance of <0.2 of the standard deviation of the logit of the propensity score, to reduce the influence of potential confounders between the two groups. The adequacy of covariates balance in the matched sample was assessed using absolute standardized mean differences (mean difference expressed in units of SMD). Covariates were selected considering the already validated prognostic scores in the perioperative setting (ASA score) and surgical setting (EuroSCORE II), and secondly, the choice of covariate was based on clinically pertinent and non-redundant variables with a higher baseline disequilibrium between the two groups. In the matched cohort, the comparison regarding the primary endpoint between the two groups of treatment was performed using the McNemar test. The treatment effect was evaluated using logistical regression. The comparison of the secondary endpoint used the McNemar test or the Wilcoxon signed-rank test. Because we tested multiple outcomes, the threshold for statistical significance was corrected by using a Bonferroni correction and set at $p < 0.01$ (0.008 divided by 6, the number of assessed outcomes). All analyses were performed using R software version 3.4.4 (R Foundation for Statistical Computing, Austria). We used the "MatchIt" package for propensity score matching. The threshold for statistical significance was set at $p < 0.05$.

Results

General population

Of the 9316 patients included during the study period, 2541 were analyzed due to the non-inclusion of 138 patients because of incomplete data and 321 patients who had intra-operative hemorrhage (Fig. 1). In the overall study population, the median age was 69 years [61–74] (males: n = 1928, 77%), and the median EuroSCORE 2 was 1.8 [0.9–3.5]. Most surgeries were valve surgery (aortic, mitral, tricuspid), coronary artery bypass graft surgery, and combined surgery (Table 1, Supplementary Tables 1 and 2).

Patients treated with norepinephrine

Of the 2541 patients, 1549 (61%) were treated with NE with a median maximal dose of 0.11 [0.06−0.2] $\mu g.kg^{-1}.min^{-1}$, and a median duration of 10 h [2–24] (Table 2). Only 25% of patients were treated for >24 h with NE. A weak correlation was demonstrated between duration and dose of NE (r = 0.474, $p = 0.0001$). Apart from the NE-treated cohort, NE was started after anesthesia induction for 889 patients (57%), during the cardiopulmonary bypass for 984 (64%) patients, and after cardiopulmonary bypass weaning for 1227 (82%) patients. NE was introduced in the ICU for 322 (18%) patients (Table 2). None were treated with vasopressin and 315 (12%) patients were treated with dobutamine.

Patients treated with NE were older with higher Euroscore 2 and ASA scores, had a higher prevalence of cardiovascular, renal and respiratory comorbidities, were more often treated with beta-blocker agents, diuretics, and angiotensin-converting enzyme inhibitor (Table 1, Supplementary Tables 1 and 2). They had more emergency surgery, endocarditis, redo surgery, coronary artery bypass graft surgery, mixed surgery, longer cardiopulmonary bypass time, higher use of Custodiol and Delnido cardioplegia, hypothermia, opioid-free anesthesia, fibrinogen and red blood cell transfusions (Supplementary Table 2).

Factors associated with norepinephrine use

Univariate analysis identified several variables that were included in the multivariate logistic regression (Supplementary Table 3). Multivariate analysis demonstrated an association between NE use and age, ASA score, chronic high blood pressure, coronary disease, dyslipidemia, right ventricular dysfunction, LVEF, hematocrit, maintenance of beta-blocker, active endocarditis, valvular aortic surgery, cardiopulmonary bypass time, Glucose-insulin-potassium use, Custodiol cardioplegia, Delnido cardioplegia, and operative fibrinogen transfusion (Supplementary Table 3, Fig. 2). The Hosmer and Lemeshow test were 9.5 ($p = 0.37$). The AUC of the model was 0.75 [95%CI:0.72−0.76], $p = 0.0001$.

Incidence of post-operative outcome according to norepinephrine use

Crude analysis demonstrated a worst post-operative course in patients treated with NE because of higher incidence of neurologic, cardiovascular, renal, and septic events and death (Supplementary Table 4). After propensity matching analysis, the use of NE was associated with a higher prevalence of composite scores in relation to a higher incidence of AKI and death (Table 3, Fig. 3). Logistic regression confirms the association between NE exposure and the composite postoperative complications (OR: 2.1 [95%CI: 1.58–3.92], $p = 0.001$). ICU and hospital length of stays were higher in patients treated with NE (Table 3).

Discussion

Our results may be summarized as follows: (1) NE is often used in cardiac surgery with cardiopulmonary bypass; (2) patients treated with NE have more comorbidities, higher medications, and more complex surgery (3) several factors (modifiable and non-modifiable) were associated with NE use, (4) patients supported by NE have a higher incidence of post-operative complications.

The present study is the first study that analyzes the use of NE from an epidemiology point-of-view in a large prospective multicentric cohort of cardiac surgical patients, out of the context of hemorrhagic shock. NE is often used for a short time (<24 h) and with low posology (<0.1 $\mu g.kg^{-1}.min^{-1}$). In >70% of the case, NE was started in the operating room. We observed a higher prevalence of NE use than that previously reported in studies evaluating vasoplegia (between 10 and 45%) [2,3,5]. Contrary to these previous studies, we observed a switch from a higher rate of NE use to phenylephrine use. The present results are in line with recent expert consensus that recommended NE as a first-line vasopressor agent [6]. A recent study performed in the United States has observed a rate of up to 90 % of vasoactive medication in cardiac surgical patients; of these medications, phenylephrine was used in 77%, and NE in 37% of the case [16].

Several factors can explain the high rate of NE use. First, several studies performed in ICU and high-risk surgical patients have demonstrated that NE is easy to use and may better improve tissue perfusion than phenylephrine [17]. Thus, in European countries, there is a switch from phenylephrine to NE, particularly in high-risk surgical populations. Second, the studied population has a higher Euroscore risk and prevalence of comorbidities than what is usually described. NE may be more often initially use as a vasopressor for blood pressure optimization than as a treatment of vasoplegic syndrome *per se*. In this way, NE infusion was started in 50% of the cases after the induction of general anesthesia. Third, as

Table 1
Demographic, medical history and treatment according to norepinephrine use.

	Overall population N = 2541	Norepinephrine free N = 992	Norepinephrine N = 1549	*p*-value
Comorbidities				
Age (years)	69 [61,74]	67 [59,73]	69 [63,75]	0.0001
Gender (male)	1928 (76)	749 (76)	1179 (76)	0.73
Body Mass Index ($kg.m^{-2}$)	27.9 [24.4,30.5]	26.8 [24,30.1]	26.8 [24,30.6]	0.02
Chronic high blood pressure	1664 (66)	634 (64)	1030 (67)	0.1
Coronary disease	1205 (48)	387 (39)	818 (52)	0.0001
Atrial fibrillation	439 (17)	127 (13)	312 (20)	0.0001
Peripheral arterial disease	240 (10)	83 (8)	157 (10)	0.14
Carotid artery stenosis	136 (5)	45 (5)	91 (6)	0.14
Stroke	204 (8)	58 (6)	146 (9)	0.001
Insulin-dependent diabetes	179 (7)	67 (7)	112 (6)	0.69
Non insulin-dependent diabetes	521 (21)	198 (20)	323 (21)	0.61
Dyslipidemia	1134 (45)	388 (39)	746 (48)	0.0001
Chronic renal failure (eGFR <60 ($mL.min^{-1}.m^{-2}$)	415 (16)	117 (12)	298 (19)	0.0001
Dialysis	20 (1)	2 (0.2)	18 (1)	0.01
Estimated glomerular filtration rate ($ml.min^{-1}.m^{-2}$)	81 [66,97]	83 [70,99]	80 [64,96]	0.001
Haematocrit (%)	41.4 [38.3, 44,3]	42 [39,45.6]	41 [37.6,44]	0.001
Left ventricular ejection fraction (%)	59 [10]	60 [10]	56 [11]	0.0001
Right ventricular dysfunction	95 (4)	20 (2)	75 (5)	0.0001
Pulmonary artery pressure (mmHg)	28 [24,32]	28 [25,35]	30 [23,40]	0.0001
Medications				
Beta-blockers	954 (38)	375 (38)	579 (37)	0.0001
Withdraw on the morning of surgery	533 (21)	132 (13)	401 (26)	
Calcium channel blockers	533 (21)	205 (20)	328 (21)	0.76
Angiotensin-converting enzyme inhibitor	548 (15)	182 (16)	366 (13)	0.001
Withdraw 24 h before surgery	354 (65)	160 (87)	194 (53)	
Amiodarone	141 (6)	44 (4)	97 (6)	0.05
Anti-aldosterone	98 (4)	27 (3)	71 (5)	0.02
Aspirin	1333 (53)	472 (48)	861 (56)	0.0001
Clopidogrel	207 (8)	75 (8)	132 (9)	0.41
Vitamin K antagonist	140 (6)	38 (4)	102 (7)	0.003
Statin	1383 (55)	485 (49)	898 (58)	0.0001
Loop diuretic	558 (22)	157 (16)	401 (26)	0.001
Insulin	179 (7)	67 (6)	112 (7)	0.69
Metformin	241 (9)	92 (9)	149 (10)	0.83
Other antidiabetic drugs	242 (9)	93 (9)	149 (10)	0.89
Scores				
Euroscore 2	1.8 [1, 3.5]	1.4 [0.8,2.5]	2.1 [1.1,4.1]	0.0001
American Society Anesthesiology score (ASA)				
1	9 (2)	7 (1)	2 (1)	
2	235 (10)	116 (12)	119 (7)	
3	1985 (79)	793 (79)	1192 (76)	0.0001
4	297 (12)	71 (7)	226 (15)	
5	15 (1)	5 (1)	10 (1)	
Type of surgery				
Urgent	347 (14)	77 (8)	270 (17)	0.0001
Preoperative sepsis	69 (3)	11 (1)	58 (4)	0.0001
Previous cardiac surgery	97 (4)	21 (2)	76 (5)	0.0001
Active endocarditis	65 (3)	8 (1)	57 (4)	0.0001
Valvular surgery	1453 (57)	629 (63)	824 (53)	0.0001
Mitral	435 (17)	142 (14)	293 (19)	0.003
Aortic	1065 (42)	503 (51)	562 (36)	0.0001
Tricuspid	155 (6)	57 (5)	98 (6)	0.61
Pulmonary	36 (2)	16 (2)	20 (1)	0.49
Coronary artery bypass graft surgery	1241 (49)	398 (40)	843 (54)	0.001
Combined surgery	780 (31)	279 (28)	501 (32)	0.02
Ascending aorta	286 (11)	121 (12)	165 (11)	0.24
Aortic arch	40 (2)	12 (1)	28 (2)	0.25
Aortic dissection	40 (2)	15 (2)	25 (2)	0.87
Others (atrial fibrillation ablation, left atrial appendage occlusion, interventricular communication, myxoma...)	227 (9)	71 (7)	156 (10)	0.01

we demonstrated an association with preoperative (right and left) cardiac function parameters, NE may also be used as a treatment for low cardiac output syndrome [18]. Fourth, we identified factors that are associated with the vasoplegic syndrome [19,20]. Some of these factors (fibrinogen transfusion, beta-blocker maintenance, GIK) may be surprising because they are the opposite of what would be expected. Previous studies have demonstrated that these factors are associated with vasomotor tone alteration and arterial hypotension [21]. Fibrinogen has several effects on microcirculation that can be more pronounced in the case of an inflammatory process [22]. Thus, fibrinogen can alter vasomotor tone. Of these factors, some factors may be modifiable, so therapeutic options can be discussed such as the treatment for anemia (patient blood management), the withdrawal of beta-blocker therapy on the morning of the surgery, the choice of cardioplegia, and the use of normothermia. Taking together these factors illustrate the high

Table 2
Vaso-active support during surgery and ICU course.

	Overall population N = 2541	Norepinephrine free N = 992	Norepinephrine N = 1549	*p*-value
Operating room				
Ephedrine	1405 (55)	466 (60.4)	446 (57.8)	0.31
Ephedrine total dose (mg)	15 [9,27]	12 [9,21]	18 [12,30]	0.88
Phenylephrine	604 (24)	215 (22)	389 (25)	0.05
Total dose (mg)	0.2 [0.1,0.4]	0.2 [0.1,0.3]	0.2 [0.1,0.4]	0.47
Norepinephrine	1227 (48)	0	1277 (82)	<0.0001
Median maximal dose ($\mu g.kg^{-1}.min^{-1}$)	0.17 [0.1, 0.28]		0.17 [0.11,0.28]	0.10
Dobutamine	256 (10)	45 (5)	211 (14)	0.0001
Median maximal dose ($\mu g.kg^{-1}.min^{-1}$)	7 [5,10]	5 [4,10]	7 [5,10]	0.98
Epinephrine	14 (1)	1 (0.2)	13 (1)	0.0001
Median maximal dose ($\mu g.kg^{-1}.min^{-1}$)	0.43 [0.18,0.64]	0.4 [0.4,0.4]	0.4 [0.16,0.67]	NA
Intensive care unit				
Norepinephrine				
Norepinephrine maximal infusion dose ($\mu g.kg^{-1}.min^{-1}$)	0.11 [0.06,0.20]	0	0.11 [0.06,0.20]	0.0001
Norepinephrine infusion time (hours)	10 [3,24]	0	10 [3,24]	0.0001
Dobutamine	315 (12)	48 (5)	265 (17)	0.0001
Dobutamine maximal infusion dose ($\mu g.kg^{-1}.min^{-1}$)	7 [5,9]	5 [4,5]	7.5 [5,10]	0.0001
Dobutamine infusion time (hours)	30 [17,60]	15 [5,34]	35 [19,362]	0.0001
Epinephrine	28 (1)		28 (2)	0.002
Epinephrine maximal infusion dose ($\mu g.kg^{-1}.min^{-1}$)	0.26 [0.08,0.92]	0	0.26 [0.08,0.92]	0.0001
Epinephrine infusion time (hours)	20 [6,40]	0	20 [6,40]	0.0001

severity of illness which is associated with chronic vasomotor tone and/or heart alterations [23,24].

Patients treated with NE have a high incidence of postoperative complications, particularly renal complications and death. We observed a higher rate of complications for reasons that are: (i) patients with a high number of risk factors are those who probably have higher severity illness, thus higher risk for postoperative complications, (ii) NE may also be the translation of an underlying abnormal process, (iii) NE may alter tissue perfusion. Literature on this subject is sparse and contradictory [25–27]. The VANCS study

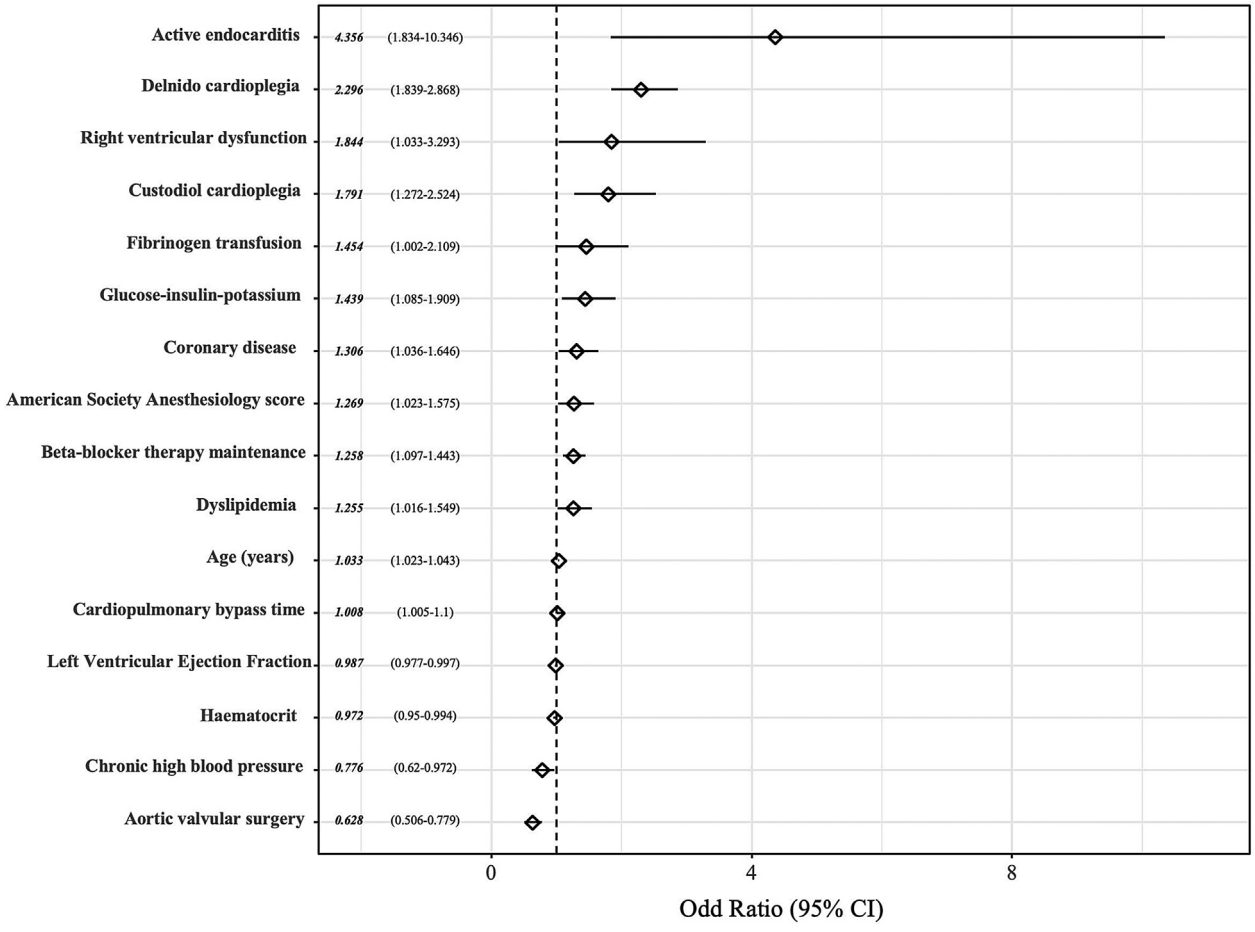

Fig. 2. Forest plot of factors associated with norepinephrine use.

Table 3
Postoperative course according to norepinephrine use, after propensity matching.

	Norepinephrine free N = 658	Norepinephrine N = 658	*p*-value
Primary endpoint			
Major adverse kidney and cerebral events	77 (12)	144 (22)	0.0001
Secondary endpoints			
Neurologic			
Stroke	12 (2)	51 (8)	0.09
Cardiac			
New episode of atrial fibrillation	164 (25)	153 (23)	
Ventricular tachycardia or ventricular fibrillation	31 (5)	29 (4)	0.39
Myocardial infarction	5 (1)	9 (2)	
Acute kidney injury	65 (10)	126 (19)	0.0001
Renal replacement therapy	4 (1)	12 (2)	
Death	3 (0.5)	16 (3)	0.005
ICU length of stays (days)	2 [2–3]	3 [2–5]	0.001
Hospital length of stays (days)	9 [7–11]	9 [7–12]	0.02

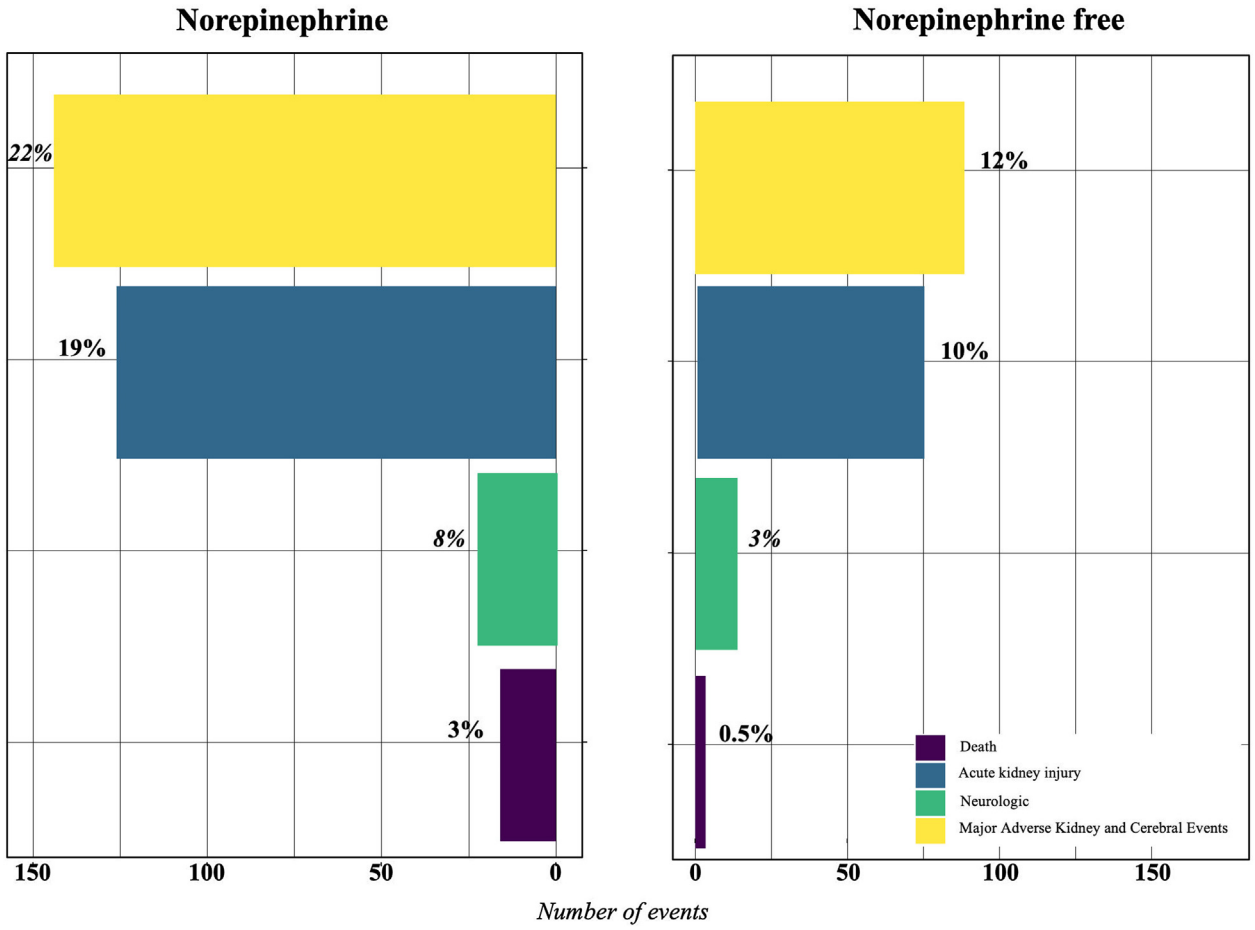

Fig. 3. Postoperative complications according to norepinephrine use in the propensity *score-matched cohort*. Major adverse kidney and cerebral events include stroke, acute kidney injury, and death.

demonstrated that NE may be associated with a higher incidence of AKI than vasopressin [9]. A randomized controlled trial demonstrated a lower complication rate with NE than with dopamine [28]. In absence of a randomized study evaluating NE against a placebo or in the context of blood pressure optimization, we cannot conclude a causal effect between NE exposure and postoperative outcomes. Our results provide data that can help the physician to design further studies focusing on vasopressor therapy, management of vasopressor [29], vasopressor sparing strategies [30], and their impact on outcomes (NCT05568160) [31]. Because we have identified several risk factors for NE use, physicians are able to select a population at high risk of postoperative complications for whom perioperative bundle care may be clinically relevant to improve peri-operative course [32,33].

The present study has limitations. This is an observational study that included a fraction of the overall surgical patients admitted during the study period, thus the study may have omitted some potential factors. We have also excluded intra-operative hemorrhagic shock and incomplete data. We observed a lower rate of

intra-operative transfusion (red blood cell or fibrinogen) than what would be expected, and we cannot exclude some bias. Risk factors were evaluated by using a multiple logistic regression model that demonstrated only association and not causation. Because of the study design, we cannot demonstrate a causal relation effect between NE and complications. The quality of the model was good, and the predictability was moderate. Further study may externally validate our results.

Conclusions

The prevalence of NE use is high for cardiac surgical patients, often used for short periods with low doses. Many preoperative and surgical factors are associated with its use. Patients treated with NE have a higher incidence of major postoperative complications.

Declarations

Ethical approval and consent to participate

This study was approved by the Institutional Review Board (CPP 2017-A01324-49) for human subjects/Independent Ethics Committee. All patients have received a written document for research purposes. The study design adheres to the requirements of the Medical Research Involving Human Subject Act and of the Declaration of Helsinki.

Author contributions

PGG designed the study, performed data analysis, and drafted the manuscript. VC, BD, VB, OAA, OB, KM, MPM, BB, MN, PGG made contribution to study conception, and data analysis. BD, VC, MPM, OAA substantially contributed to data collection. All the authors approved the final version of the paper.

Funding

None to declare.

Ethical statement

We performed a multicenter observational prospective study that was approved by the French ethical committee (Comité De Protection Des Personnes Sud Mediterranee I, 2017-A01324-49, Chairman: Pr Y. JAMMES) for human subjects. The study was conducted in the anesthesia and critical care cardiac surgical department of the university-affiliated tertiary hospitals of Dijon, Amiens, Rouen and Strasbourg, France, from 2017 to 2021. All patients have received a written document for research purposes, and gave their consent prior to participate. The study design adheres to the requirements of the Medical Research Involving Human Subject Act and of Declaration of Helsinki. The study complied with STROBE guidelines

Conflict of interest

None.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Acknowledgements

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2023.101200.

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