BMJ Open

Norepinephrine weaning guided by the Hypotension Prediction Index in vasoplegic shock after cardiac surgery: protocol for a single-centre, open-label randomised controlled trial – the NORAHPI study

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To cite: Beyls C, Lefebvre T, Mollet N, *et al*. Norepinephrine weaning guided by the Hypotension Prediction Index in vasoplegic shock after cardiac surgery: protocol for a single-centre, open-label randomised controlled trial – the NORAHPI study. *BMJ Open* 2024;**14**:e084499. doi:10.1136/bmjopen-2024-084499

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2024-084499).

Received 20 January 2024
Accepted 04 June 2024

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ABSTRACT

Introduction Norepinephrine (NE) is the first-line recommended vasopressor for restoring mean arterial pressure (MAP) in vasoplegic syndrome (vs) following cardiac surgery with cardiopulmonary bypass. However, solely focusing on target MAP values can lead to acute hypotension episodes during NE weaning. The Hypotension Prediction Index (HPI) is a machine learning algorithm embedded in the Acumen IQ device, capable of detecting hypotensive episodes before their clinical manifestation. This study evaluates the clinical benefits of an NE weaning strategy guided by the HPI.

Material and analysis The Norahpi trial is a prospective, open-label, single-centre study that randomises 142 patients. Inclusion criteria encompass adult patients scheduled for on-pump cardiac surgery with postsurgical NE administration for vs patient randomisation occurs once they achieve haemodynamic stability (MAP>65 mm Hg) for at least 4 hours on NE. Patients will be allocated to the intervention group (n=71) or the control group (n=71). In the intervention group, the NE weaning protocol is based on MAP>65 mmHg and HPI<80 and solely on MAP>65 mm Hg in the control group. Successful NE weaning is defined as achieving NE weaning within 72 hours of inclusion. An intention-to-treat analysis will be performed. The primary endpoint will compare the duration of NE administration between the two groups. The secondary endpoints will include the prevalence, frequency and time of arterial hypotensive events monitored by the Acumen IQ device. Additionally, we will assess cumulative diuresis, the total dose of NE, and the number of protocol weaning failures. We also aim to evaluate the occurrence of postoperative complications, the length of stay and all-cause mortality at 30 days.

Ethics and dissemination Ethical approval has been secured from the Institutional Review Board (IRB) at the University Hospital of Amiens (IRB-ID:2023-A01058-37). The findings will be shared through peer-reviewed publications and presentations at national and international conferences.

Trial registration number NCT05922982.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The prospective, monocentric, open-label, randomised trial will include 142 patients scheduled for cardiac surgery under cardiopulmonary bypass.
⇒ Patients with vasoplegic syndrome requiring norepinephrine (NE) will be included.
⇒ In the intervention group, NE weaning will be guided by mean arterial pressure and the Hypotension Prediction Index.
⇒ The primary endpoint will be the duration of NE administration.
⇒ The secondary endpoints will include the number of NE weaning protocol failures, total NE dose, diuresis, cumulative fluid volume and postoperative complications.

BACKGROUND

The vasoplegic syndrome (VS) is characterised by an arterial hypotension (mean arterial pressure (MAP)<65 mm Hg), a decrease in vascular resistance and a normal or increased cardiac output[1] vs increases the morbidity and mortality of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).[2] This syndrome is a common postoperative complication, with an incidence rate ranging from 9% to 44%, and multiple well-established prognostic factors have been identified.[3]

Norepinephrine (NE) is recommended as the first-line vasopressor therapy for restoring MAP.[4] However, caution is crucial, as excessive NE dosing or prolonged exposure can lead to adverse outcomes.[5] The goal of NE sparing or weaning is to minimise exposure while avoiding episodes of arterial hypotension. The administration and management of NE are carried out daily by qualified intensive

care unit nurses (ICU nurses) under medical prescription. Several studies have demonstrated that the implementation of protocols[6 7] managed by ICU nurse allows a better compliance to the therapy and ICU course. The titration of NE dose (increase or decrease) is based on a department protocol to target a prefixed blood pressure (either systolic or mean). Recently, a multicentric prospective study evaluating the impact of nurses' interventions in the weaning of NE guided by protocolsrevealed an inverse relationship between the duration of NE administration and the number of interventions by ICU nurses. This suggests the crucial role of ICU nurses in guiding NE weaning protocols to reduce NE exposure.[8] However, managing NE solely based on a target MAP value can lead to arterial hypotension, necessitating frequent haemodynamics adjustments.

The Acumen IQ device (Edwards Lifesciences, Irvine, California, USA) is an invasive haemodynamic monitoring system connected to an arterial catheter and equipped with a machine-learning algorithm that calculates a predictive index for episodes of arterial hypotension (Hypotension Prediction Index, HPI).[4] HPI monitors the patient's haemodynamics, detects hypotensive events a few minutes before they occur and allows for intervention to prevent the arterial hypotensive event. In some studies, HPI has been shown to reduce hypotensive events by 57%.[9 10] HPI is graded from 0 to 100 without units, with a predictive threshold for hypotension set at 80.[11] HPI has never been used in the context of NE weaning. HPI also monitors other haemodynamic indices that assess the patient's preload dependency. In the case of arterial hypotension, correcting this preload dependency through intravascular fluid administration can improve NE weaning. HPI could enhance NE weaning by preventing episodes of arterial hypotension or detecting preload dependency, thereby avoiding any transient increase in NE in case of hypotension.

The aim of our study is to evaluate the clinical benefits of NE weaning using an interventional haemodynamic algorithm guided by the HPI.

METHODS AND ANALYSIS

Study design

This is a monocentric, prospective, open-label, randomised study.

Study population

The inclusion criteria will be:

- Patients aged more than 18 years old.
- With a vs exposed to NE for at least 4 hours within 48 hours of ICU admission.
- After a scheduled cardiac surgery under CPB (coronary artery bypass grafting, valve replacement, ascending aorta replacement or combined surgery (valve and bypass grafting)).
- To be entitled to the French national health service (Sécurité Sociale).
- Preoperative signature for the consent to participate in the study.

The exclusion criteria will be:

- Permanent arrhythmia (atrial fibrillation, flutter or frequent atrial extrasystoles).
- Treatment with dobutamine, epinephrine or vasopressin analogue.
- Patients with preoperative chronic end-stage renal failure who require postoperative extrarenal purification.
- Pregnancy.
- The patient is dependent on an internal or external pacemaker.
- Hypothermia <36°C.
- Patient under mechanical circulatory assistance after cardiac surgery.
- Active postoperative bleeding.
- Inclusion in another study within the last 30 days.
- Patient under guardianship or curatorship.

Study protocol

Randomisation

Randomisation will be conducted by the physician in the cardiac, thoracic, vascular and respiratory ICU (CTVR-ICU) once the patient meets the inclusion criteria. Patients will be randomised into two parallel open-label groups using a minimisation algorithm with two strata: Euroscore II and the NE dose at inclusion. The randomisation process will be executed by a data manager using Ennov Clinical software. The patient will be allocated to either the ''sandard group' or the 'intervention group' (see figure 1).

Standard care in both groups

In both groups, the conditions for administering NE, such as dilution, infusion rate and NE relay, will follow the local protocol dedicated to patients with postoperative vs in our ICU at Amiens University Hospital and remain consistent with the practices observed beyond the scope of this research study.

In each group and following randomisation, all patients will have an Acumen IQ device connected to either the radial or femoral arterial catheter at the discretion of the clinician in charge. The arterial catheter will be inserted in the operating room under general anaesthesia as part of cardiac surgery procedure. The Acumen IQ device will be linked to the HemoSphere monitor platform (Edwards Lifesciences) to collect all haemodynamic measurements for assessing primary and secondary endpoints. Each nurse intervention (adjustment of NE doses or administration of fluids) is electronically recorded in our healthcare system software and in the HemoSphere monitor. In the standard group, HPI value will not be available on the HemoSphere monitor screen, but the values will be recorded throughout the entire duration of the research protocol.

During the study protocol, in the event of haemodynamic deterioration, all patients will undergo an

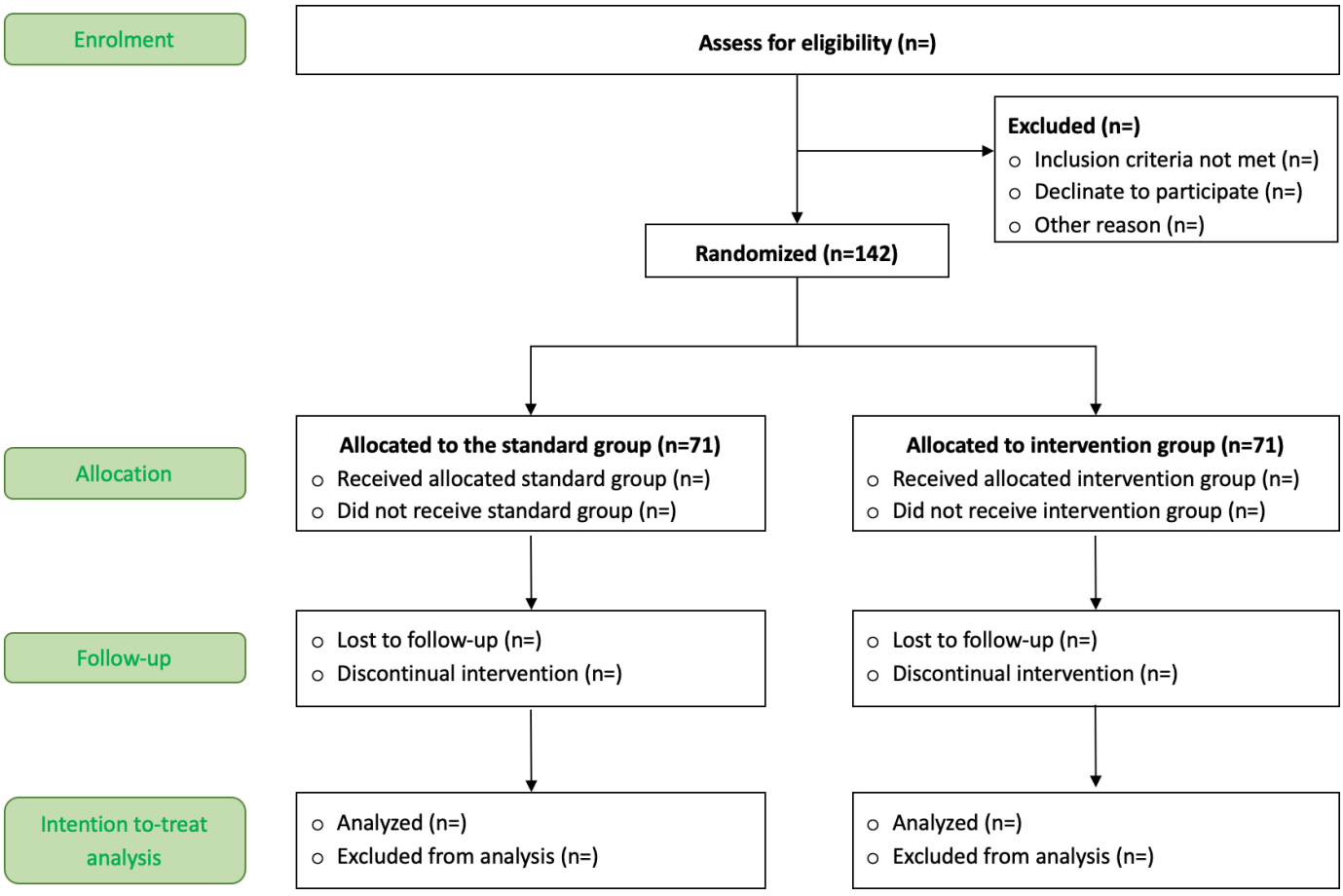

Figure 1 CONSORT diagram. CONSORT, Consolidated Standards of Reporting Trials.

echocardiographic evaluation to detect any surgical complications and to assess the haemodynamic status. The preload dependency will be evaluated through a passive leg-raising test.[12] If the test yields a positive result with a stroke volume variation >15% on the Acumen IQ monitoring, the patient will receive fluid resuscitation with crystalloids or colloids. In case of a negative result, the attending physician may increase NE or introduce a new catecholamine based on the haemodynamic assessment. The research protocol's duration for each patient is 72 hours. Beyond this time frame, if the administration of NE persists, it will be categorised as an NE weaning failure.

Intervention group

In the intervention group, the weaning of NE will be guided by the HPI and MAP provided by the Acumen IQ (figure 2A) device and the HemoSphere monitor (figure 2B).

During each clinical round conducted, which occurs every 2 hours, the nurse may gradually reduce the NE infusion by 0.01 µ/kg/min if the MAP is ≥65 mm Hg and the HPI is <80%. The HPI value will be an average calculated over 10 min and provided by the HemoSphere monitor. Following each step of NE weaning, there will be a 10 min monitoring period before proceeding to the next step. The maximum allowable decrease during the nurse's round is 0.03 µ/kg/min of NE. If arterial hypotension occurs during these weaning steps, the nurse may increase NE by 0.01 µ/kg/min (figure 3A).

Standard group

In the standard group, the weaning process of NE will be guided by the MAP provided by the Acumen IQ device and the HemoSphere monitor. HPI function of the Acumen IQ device will be disabled on the HemoSphere screen, but HPI values will be recorded alongside other haemodynamic parameters. During each clinical round conducted by the nurse, which occurs every 2 hours, the nurse may gradually reduce NE infusion by 0.01 µ/kg/min if the MAP is ≥65 mm Hg. Following each step of NE weaning, there will be a 10 min monitoring period before proceeding to the next step. The maximum allowable decrease during the nurse's round is 0.03 µ/kg/min of NE. If arterial hypotension occurs during these weaning steps, the nurse may increase NE by 0.01 µ/kg/min (figure 3B).

Outcome measures

Primary endpoint

The endpoints and definitions are presented in table 1.

The primary endpoint is comparing the duration of NE administration between the two groups. The duration will be defined as the difference in time between the

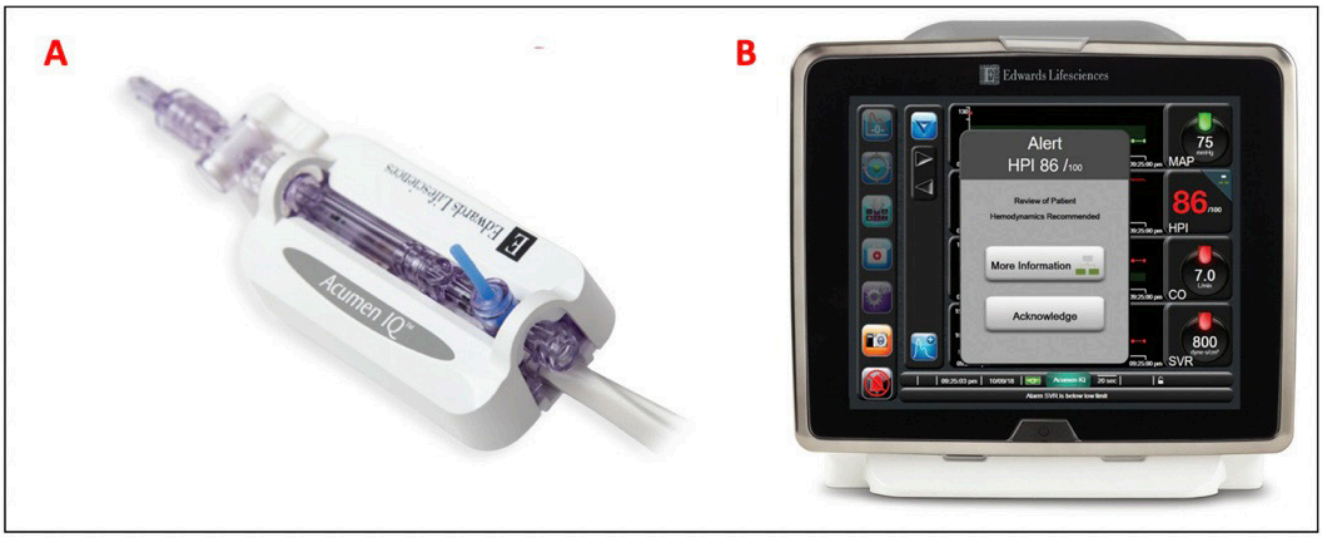

Figure 2 (A) The Acumen IQ device, integrated with the arterial catheter. (B) Continuous monitoring and collection of haemodynamic parameters via the HemoSphere monitor.

beginning of the study (day 0) and the end of the study protocol (day 3).

Secondary endpoints

The secondary endpoints encompass several aspects, including the number of failures in the NE weaning protocol and the prevalence, frequency and duration of hypotensive episodes monitored via the Acumen IQ device. Additionally, we aim to assess the total amount of NE administered during the research protocol. Cumulative diuresis and volume of crystalloids, colloids or blood products administrated will also be evaluated during the protocol from day 0 to day 3 and when NE weaning is deemed successful. Furthermore, we will examine the incidence of postoperative complications as defined by the European Society of Anesthesia and Resuscitation, which includes neurological, respiratory, cardiovascular, renal, digestive, haemorrhagic and infectious complications. Other outcomes to be studied will encompass the length of stay in the ICU and in the hospital and all-cause mortality at day 30.

Data collection and outcome definition

The following data will be collected: age (years), gender, body mass index (kg/m²), medical history (coronary disease, peripheral vascular disease, stroke, smoking, diabetes, dyslipidaemia, chronic obstructive pulmonary disease, logistic EuroSCORE II, hypertension,

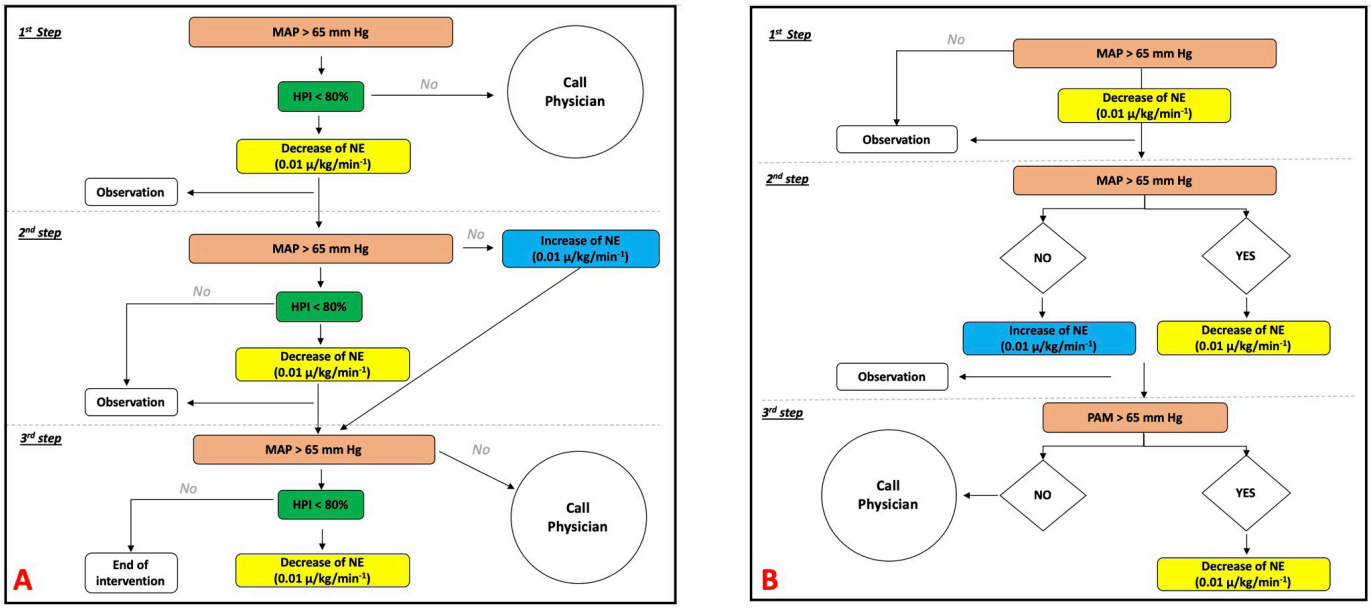

Figure 3 Protocol steps of the intervention group (A) and the standard group (B). HPI, Hypotension Prediction Index; MAP, mean arterial pressure; NE, norepinephrine.

Table 1 Endpoints and definitions

Endpoints	Definitions
Primary endpoint at day three after cardiac surgery	
Duration of NE administration	Difference in time (hours) between the beginning of the study (day 0) and the end of the study protocol (day 3)
Secondary endpoints	
Number of failures in the NE weaning protocol.	Failure being defined as the persistence of NE delivery 72 hours after inclusion.
Prevalence, frequency and duration of hypotensive episodes monitored by the Acumen IQ device.	Hypotension is defined by the presence of a mean arterial pressure <65 mm Hg for a minimum duration of 30 s. Blood pressure must be invasive and monitored on the HemoSphere monitor.
NE total dose	NE total dose delivered during the research protocol phase (mg/kg) automatically calculated by the DianeRea software (BowMedical, France).
Cumulative diuresis	Cumulative diuresis (ml/kg/hour) during the study protocol or when NE weaning is considered a success.
Volume of administrated fluids	Cumulative volume of administration of crystalloids, colloids or blood products during protocol or when NE weaning is considered as successful
Postoperative complications	
Stroke	Any embolic, thrombotic or haemorrhagic cerebral event with persistent residual motor, sensory or cognitive dysfunction (eg, hemiplegia, hemiparesis, aphasia, sensory deficit, impaired memory) diagnosed on a cerebral scanner
Myocardial infarction	Myocardial infarction diagnosed by the clinical presentation, serial changes on 12-lead electrocardiographic suggesting infarction and rise in cardiac markers (preferably cardiac troponins) with at least one value above the 99th percentile of the upper reference limit
Resuscitated cardiac arrest	Cessation of mechanical cardiac activity confirmed by the absence of clinical signs of blood flow
Acute kidney injury	KDIGO guidelines Increase in serum creatinine of over 27 µmol/L within 48 hours or diuresis lower than 0.5 mL/kg/hour
Mesenteric ischaemia	Mesenteric ischaemia confirmed by imaging or exploratory laparotomy and/or ischaemic colitis confirmed by gastrointestinal endoscopy or exploratory laparotomy
In-hospital mortality	Mortality from surgery to hospital discharge
30 days hospital mortality	Mortality after surgery until 30 days follow-up

KDIGO, Kidney Disease Improving Global Outcomes; NE, norepinephrine.

chronic kidney disease, usual medication, surgery type (valve replacement, coronary bypass graft or combined surgery), preoperative left ventricular ejection fraction, baseline haemoglobin, duration of CPB and aortic clamp, intraoperative transfusion and cumulative dose of NE.

After CPB and until the conclusion of the research protocol, the Acumen IQ device will record the following data: systolic arterial pressure, diastolic arterial pressure, MAP, heart rate, cardiac output, stroke volume, dynamic elastance, systolic slope (dP/dT), dynamic arterial elastance (Ea_{dyn}), stroke volume variation, systemic vascular resistance and pulse pressure variation.

The following biological data will be collected after CPB and during the research protocol: arterial blood gas variables (pH, PaO2, PaCO2, lactate, HCO3), ScVO2 (%), SOFA score, NE dose and biological variables (creatinine, aspartate aminotransferase, alanine aminotransferase, prothrombin time, platelet count, cardiac troponin, myoglobin).

After CPB and at the end of the research protocol, transthoracic echocardiography will be performed and the following data will be collected: left ventricular ejection fraction, parameters of diastolic function, paravalvular leak, size and volume of cardiac chambers, parameters of right systolic function, size and collapsibility of the inferior vena cava and the presence of pericardial effusion.

The primary endpoint will be assessed when the NE weaning protocol is considered successful or at the end of the research protocol (72 hours after randomisation). The secondary endpoints will be assessed at 30 days. Any clinical adverse events will be documented and reported in the electronic case report forms (eCRFs).

Standard definitions of postoperative outcomes established by the European Society of Anesthesia[13] will be

used. Cardiac arrest is defined as the cessation of mechanical cardiac activity, confirmed by the absence of signs of circulation. Stroke is defined as an embolic, thrombotic or haemorrhagic cerebral event resulting in persistent motor, sensory or cognitive dysfunction (eg, hemiplegia, hemiparesis, aphasia, sensory deficits, impaired memory), as diagnosed through cerebral CT scanning. Acute kidney injury (AKI) follows the Kidney Disease Improving Global Outcomes criteria, characterised by an increase in serum creatinine of over 27 µmol/L within 48 hours or a diuresis rate lower than 0.5 mL/kg/hour. Myocardial injury is diagnosed based on specific clinical presentation, serial changes in the 12-lead ECG indicative of infarction and an increase in cardiac troponin levels, with at least one value exceeding the 99th percentile of the upper reference limit. Mesenteric ischaemia is diagnosed through imaging or exploratory laparotomy while ischaemic colitis is confirmed via gastrointestinal endoscopy or exploratory laparotomy. Mediastinitis was defined by CT imaging and bacterial documentation. The length of stay in ICU and in hospital (in days) and all-cause mortality will be assessed at the 30-day mark.

Intention-to-treat analysis

Patients experiencing significant clinical adverse events will be analysed according to the group they were initially assigned to (standard or interventional group) by the intention-to-treat principle.

Statistical method and sample size calculation

For the primary endpoint, the null hypothesis (the duration of NE administration is the same between the two groups) will be rejected in favour of the alternative hypothesis (there is a difference) using an independent samples t-test (or Mann-Whitney test depending on the normality of the data) with a two-tailed alpha level of 5%. An analysis of covariance model will validate the difference between the two groups after adjusting for Euroscore II and the NE dose at randomisation. An analysis of variance tests for repeated haemodynamic measures will be used for the secondary endpoints. The number of failures in the weaning NE protocol, postoperative complications and mortality rate will be compared using a χ^2 test. The total dose of NE, cumulative diuresis, fluids administered during the NE weaning protocol, ICU and hospital stay will be compared using a Student's t-test. (or the Mann-Whitney test, depending on the normality of the data. A p value of 0.05 will be considered significant. No interim analysis is planned in the trial.

Sample size calculation

According to a previous study, the SD of the duration of NE administration in patients with vs postcardiac surgery was 6 hours.[14] Therefore, to demonstrate a difference of 3 hours between the two groups, it is necessary to include 128 patients. These calculations were performed with a two-tailed alpha level of 5% and a power of 80%. Considering that 10% of patients may not be evaluable for the primary criterion, 142 patients will be included. Amiens University Hospital annually conducts approximately 550 cardiac surgery procedures with on-pump CPB surgery. A recent study conducted at our centre revealed an incidence of 30% of vs following cardiac surgery. Assuming that 50% of vs cases will meet eligibility, the criteria suggest a potential enrolment of 82 patients annually. Considering possible exclusions due to vacations and operating room closures, we anticipate a total enrollment period of 24 months, with a target of 142 patients (71 patients in each group—standard and interventional).

Data management and monitoring

Registration

Haemodynamic measurements for each patient will be exported from the HemoSphere monitor via USB as a Microsoft Excel (Microsoft Corporation, Redmond, Washington, USA) xls files and will be analysed with the Acumen Analytics (Edwards Lifesciences) software package. The haemodynamic monitoring data collected by the Acumen IQ device during the protocol research will be saved in the eCRF for each patient. A specialised local research technician will be responsible for gathering and inputting the data using eCRFs while a research coordinator will oversee the centralisation and validation of the collected information.

Record keeping

The University Hospital of Amiens will retain consent documents and eCRFs for 15 years by French law.

Study organisation

The Clinical Research and Innovation Directorate of the University Hospital of Amiens, France, promotes the study.

Duration and timeline

Starting in January 2024, patients from the Amiens University Hospital can be enrolled over 2 years. Protocol development, ethical committee approval, financial support and eCRF development were completed in 2023. The database will be closed once all participants are enrolled, after which, data analysis, manuscript writing and submission for publication will follow.

ETHICS AND DISSEMINATION

The Noraphi study is an open-label randomised study conducted at Amiens University Hospital, France, in the CTVR-ICU. The institutional review board (IRB) at the University Hospital of Amiens (ID-IRB: 2023-A01058-37) and the Comité de Protection des Personnes (Île-de-France I, 75000 Paris, France) approved the study (Registration ID: CPPIDF1-2023-DI47-IC-Cas4.2) on 8 August 2023. The Noraphi study will be conducted in accordance with the Declaration of Helsinki and French interventional clinical research laws.[15] According to French law governing interventional clinical research studies, both oral and written information is provided to the patients,

and obtaining written informed consent from all participants is a requirement. The Norahpi study follows the strengthening of reporting guidelines for parallel group randomised trials (see figure 1).[16] The Norahpi study was registered on ClinicalTrials.gov (trial ID: NCT05922982) on 23 June 2023. The authors will actively participate in sharing research findings by attending conferences and collaborating as coauthors on publications of the results.

Patients or public involvement

Patients or the public will not be involved in our research's design, conduct, reporting or dissemination plans. Written informed consent will be obtained from all participants (patient consent in online supplemental file 1).

DISCUSSION

The hypothesis is that HPI-guided NE weaning will reduce the duration of NE administration while preventing episodes of arterial hypotension and optimising the patient's fluid balance. Moreover, we hypothesise that reduced NE exposure could be associated with less organ injury, such as AKI or myocardial infarction.

In the acute phase of vs, fluid and NE administration are necessary to achieve haemodynamic stability and tissue perfusion. Excessive exposure to NE can lead to organ dysfunction, particularly AKI.[5] In addition, the haemodynamic instability may be associated with altered preload, compensated by the 'fluid-like effect' of NE, and physicians may arbitrarily infuse more fluid for NE weaning more rapidly. However, this can result in fluid overload.[17] During NE weaning, episodes of arterial hypotension could lead to adverse clinical events. In a large retrospective study, the authors suggested that every 5 mm Hg decrease in MAP below 65 mm Hg is associated with adverse clinical events.[18] So, to prevent organ damage resulting from these different mechanisms (arterial hypotension, increased fluid balance, prolonged exposure to NE), several studies have been conducted to evaluate NE weaning protocols based on haemodynamic parameters beyond MAP.

In a study by Guinot *et al*, 130 patients experienced vs following cardiac surgery. A haemodynamic protocol for NE weaning based on dynamic arterial elastance was associated with a reduction in NE administration duration (17 (13–26) hours vs 39 (19–59) hours; p<0.0001).[19] Furthermore, a post hoc analysis of this study reported an association between NE exposure and the occurrence of AKI.[20] Recently, a study in major non-cardiac surgeries where a haemodynamic protocol used the HPI showed a significant reduction in the number and duration of hypotensive events.[21]

However, to date, no data are available regarding the impact of a haemodynamic algorithm incorporating the HPI in the context of NE weaning. This pilot study represents an important preliminary step before conducting a larger prospective multicentre randomised study in the field

Trial status

The trial has been recruiting since 14 December 2023.

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Contributors CB, OA-A and YM participated in the study's design and helped to write the manuscript. TL, NM and AB participated in the design of the study. JM will perform the statistical analysis. All authors read and approved the final manuscript.

Funding The Norahpi trial was supported by Amiens University Hospital, grant number ID-IRB: 2023-A01058-37.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Consent obtained directly from patient(s).

Provenance and peer review Not commissioned; externally peer reviewed.

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