Intraoperative norepinephrine to prevent intraoperative arterial hypotension in patients at increased risk of postoperative complications:
A multicenter prospective randomized trial

The INPRESS trial – Intraoperative Norepinephrine to control arterial PRESSure

Version: 9 Date: 07/06/2016

EudraCT identifying number 2011-004232-66
Clinicaltrials.gov NCT01536470

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Study rationale / Scientific background and hypothesis

- Background (current state of scientific knowledge)
  The intraoperative period is characterized by hemodynamic instability and intraoperative hypotension is a common complication during surgery and general anesthesia. Various definitions of intraoperative hypotension have been evaluated in the literature, resulting in a widely varying incidence of hypotension (5% to 75%).
  This has obvious important clinical consequences, especially in the estimated association between hypotension and patient outcome. A large survey of anesthesia-related mortality in France found that, among perioperative death partially or related to anesthesia (5.4 in 100000 patients), 39% were the consequence of inadequate management of intraoperative hypotension.

  Several studies have shown that intraoperative hypotension may be an important determinant of postoperative complications after noncardiac surgery. Arterial pressure is a key determinant of tissue pressure. Intraoperative hypotension may contribute to oxygen supply-demand mismatch and tissue hypoperfusion, and has the potential to cause an ischemia-reperfusion injury, systemic inflammatory response syndrome (SIRS) and postoperative organ dysfunction, especially acute kidney injury, which is associated with considerable morbidity and mortality. The clinical importance of SIRS on the development of organ dysfunction following surgical stress and trauma, although suggested in previous studies, still remains debated. It has previously been suggested that SIRS may be regarded as an entry stage of organ dysfunction, with a hierarchical progression from SIRS to deteriorated organ function and refractory organ failure. Finally, data from a recent large cohort study including 1,705 consecutive adult patients have suggested that intraoperative hypotension may be associated with an increase in 1-yr mortality in elderly patients after noncardiac surgery. However, although adjustments were made for important confounding variables, residual confounding (doses of anesthetics, depth of intraoperative anesthesia, intraoperative hemodynamic management) was inevitable and precludes any definitive conclusion.

  Among other risk factors, the use of antihypertensive medications (angiotensin-converting enzyme inhibitor [ACEI], angiotensin II receptor antagonist [AIIRA], …), advanced age, and cardiovascular comorbidities (especially chronic hypertension) are frequently found to be associated with an increased risk of intraoperative hypotension. The duration of intraoperative hypotension plays also a central role in the pathogenesis of hypotension during surgery. General anesthesia, especially during the induction period, is responsible an increased risk of hypotension because of the hemodynamic effects of most anesthetic agents. In a recent study including 4,096 patients, Reich and colleagues found that 9% of patients experienced severe hypotension (defined as mean arterial pressure [MAP] <60 mmHg or MAP decrease of >40% and MAP <70 mmHg) within 10 min postinduction of general anesthesia. In a retrospective analysis of a large database from two university teaching hospitals in France the incidence of hypotension was 16.8%.

  There is no consensus on the definition of intraoperative hypotension, which is commonly defined as a systolic blood pressure (SBP) lower than 80 mmHg or a decrease of SBP >40% or a combination of both. In an observational study of 1,705 consecutive adult patients who underwent general and vascular surgery, Bijker and colleagues found that, although not statistically significant, the risk of dying within 1 yr
after surgery seems to increase when the threshold value of intraoperative hypotension was below a SBP of 80 mmHg or a MBP of 60 mmHg or when there was a decrease in both systolic and mean blood pressure of 40-45% from baseline.

Finally, there is also no clear evidence regarding optimal treatment strategy for intraoperative hypotension during general anesthesia. Sympathetic adrenoreceptor agonists (e.g., ephedrine chloride) are considered the standard treatment for anesthesia-induced hypotension, in addition to the correction of intravascular volume deficits using fluid loading. Because the sympathetic system is impaired by general anesthesia, the use of terlipressin (Glypressine®) was suggested as the ideal drug to treat hypotension, especially in patients with long-term ACEI or AII-R treatment. Although terlipressin was found to be effective for the treatment of hypotension in anesthetized patients, terlipressin is associated with negative effects on gastric mucosal perfusion and an increased risk of iatrogenic oxygen supply dependency.

Phenylephrine is a selective alpha-1 adrenergic agonist which is widely used to control arterial pressure during general anesthesia but may expose patients to transient impairment of left ventricular global function, especially in those with coronary artery disease. In an experimental model of abdominal surgery, Hiltebrand and colleagues found that increasing systemic pressure with norepinephrine (to 65 and 75 mmHg) in the setting of fluid-restricted surgery had no adverse effects on microcirculatory blood flow or tissue oxygen tension in the intestinal tract. To date, however, there is a lack of data from clinical trials on the benefit to maintain tissue perfusion and to prevent arterial hypotension with continuous intravenous infusion of norepinephrine, as compared with the standard practice of a curative treatment.

The accumulating evidence that intraoperative hypotensive may contribute to morbidity and mortality in surgical patients justifies a randomized controlled trial to evaluate whether a preventive treatment strategy using continuous infusion of norepinephrine to control arterial pressure and to maintain tissue perfusion could reduce the postoperative morbidity, compared with routine practice.

- **Hypothesis**
  We hypothesized that an individualized preventive treatment strategy to maintain arterial pressure within usual patient’s range using an intravenous infusion of norepinephrine could reduce organ dysfunction as compared with intravenous boluses of ephedrine to treat arterial hypotension.

**Summary of the benefits and foreseeable and known risks for subjects participating in the research**
In France, over 10 million general anesthesia for surgery are performed annually. The number of patients undergoing major surgery is growing continuously with advancements in treating disease. However, many patients still continue to die or suffer severe postoperative complications. Postoperative complications reduce both life expectancy and quality of life, and increase costs of care. Although the exact incidence of hypotension during general anesthesia is unknown and an association between hypotension and adverse outcomes or higher 1-yr mortality remain debatable, early and efficient therapeutic strategies to treat potential triggers of organ failures, such as tissue hypoperfusion, is particularly important especially in high-risk surgical population.
There should be no serious adverse events (SAEs) for patients in this research. Most adverse events with norepinephrine are benign and transient. However, in the context of surgery, special attention will be given to:

- Intraoperative bradycardia
- Intraoperative bleeding

**Study objectives**

**Primary objective**
To assess the effects of an individualized preventive treatment strategy to maintain SBP within ±10% of the patient resting blood pressure (used as the reference value) using a continuous infusion of norepinephrine with that of standard practice (curative treatment strategy of intraoperative hypotension defined as any drop in SBP below 80 mmHg or a decrease of SBP >40% from reference value using intravenous boluses of ephedrine) on postoperative organ dysfunctions.

**Secondary objectives**
- To determine the effect of the individualized preventive treatment strategy on the incidence of intraoperative hypotension and hypertension
- To evaluate the effect of the individualized preventive treatment strategy on intraoperative arterial pressure variability (area under the curve)
- To evaluate the effect of the individualized preventive treatment strategy on postoperative rehabilitation (time to return of bowel function, incidence of postoperative nausea and vomiting)
- To evaluate the effect of the individualized preventive treatment strategy on the requirement for blood transfusion
- To evaluate the effect of the individualized preventive treatment strategy on intraoperative volume of fluids (crystalloid and colloid)
- To evaluate the effect of the individualized preventive treatment strategy on postoperative morbidity
- To evaluate the effect of the individualized preventive treatment strategy on the duration of hospital stay
- To evaluate the effect of the individualized preventive treatment strategy on the duration of postoperative mortality
Study design
The Intraoperative Norepinephrine to control arterial PRESSure (INPRESS) trial is a multicenter, prospective, randomized, stratified, parallel-group clinical trial with concealed allocation of patients at high-risk of postoperative complications after abdominal surgery in a 1:1 ratio to a standard or an individualized treatment strategy:

- Control group = standard (curative) treatment strategy
  In the standard treatment group, patients will receive intravenous boluses of ephedrine to treat any drop in SBP below 80 mmHg or lower than 40% from the patient resting blood pressure (used as the reference value)

- Intervention group = individualized (preventive) treatment strategy
  In the individualized treatment group, patients will receive continuous infusion of norepinephrine to maintain SBP within ±10% of the patient resting blood pressure (used as the reference value)

In the two treatment groups, the patient resting blood pressure will be used as the reference value. If not available, the blood pressure value obtained in the surgical ward the day before surgery (after a 5-min rest while lying supine) will be used as reference value.

Study population
- Inclusion criteria
  1. Adult patients older than 50 years
  2. Scheduled for major abdominal or non-abdominal surgery
  3. Expected surgical duration of at least 2 hours
  4. American Society of Anesthesiologists (ASA) physical status (ASA class II or higher)
  5. Acute Kidney Injury (AKI) risk index^9 (4 or more of the following):
     a. Age ≥56 years
     b. Male sex
     c. Congestive heart failure
     d. Chronic hypertension
     e. Emergency surgery
     f. Abdominal surgery
     g. Ascites
     h. Renal insufficiency-mild or moderate (preoperative serum creatinine value >1.2 mg/dl or >105.6 μmol/l)
     i. Diabetes mellitus-oral or insulin therapy

- Exclusion criteria
  1. Severe untreated or uncontrolled hypertension despite medications
  2. Chronic kidney disease with glomerular filtration rate <30 ml/min/1.73 m2 or requiring renal-replacement therapy for end-stage renal disease
  3. Acute cardiovascular event, including acute or decompensated heart failure and acute coronary syndrome
  4. Renal vascular surgery
  5. Preoperative sepsis
  6. Circulatory shock
  7. Preoperative norepinephrine infusion before study entry
8. Surgical procedure under regional anesthesia (both epidural and spinal anesthesia)
9. No affiliation with the French healthcare system
10. Participation in another competing interventional study
11. Refusal to participate
12. Pregnant or breastfeeding women

- **Study discontinuation and patient withdrawal**
  The study will be overseen by a steering committee and a data monitoring and safety committee (DMSC). The steering committee will be jointly responsible with the independent DMSC for safeguarding the interests of the participating patients. Recommendations for pausing or stopping the study will be made by the DMSC in case of safety reasons (group-difference is found in suspected unexpected serious adverse reactions or serious adverse events). The steering committee will be responsible to continue, hold or stop the study based on the DMSC recommendations.

Patients may be withdrawn from the study if the patient withdraw consent. Patients who will withdraw from the study will be followed up until hospital discharge, according to routine clinical practice in each participating center. Patients will be asked for permission to use data obtained prior to withdrawal and to obtain data for the primary outcome measure. If this is achieved the patient will be included in the final analyses. If the patient declines, all data from that patient will be destroyed and a new patient will be randomized to obtain the full sample size.

- **Exclusion period and participation to other research**
The participation to other research is not allowed during the study period (31 days).

- **Financial compensation for participants**
There will be no financial compensation for participants.

**Study outcomes**

- **Primary outcome**
The primary outcome measure will be a composite of systemic inflammatory response syndrome (SIRS) and at least one major organ dysfunction for renal, cardiovascular, respiratory, neurologic and coagulation systems by day 7 after surgery.

- **Secondary outcomes**
  - Incidence of intraoperative hypotension (SBP <80 mmHg or decrease >40% from reference value)
  - Incidence of intraoperative arterial hypertension (SBP >160 mmHg and/or DBP >90 mmHg)
  - Incidence of severe bradycardia (heart rate <40 beats per min)
  - Intraoperative arterial pressure variability (area under the curve)
  - Volume of blood loss and number of units of packed red blood cells administered during surgery
  - Urinary output on postoperative day 1 and day 2
  - RIFLE and AKIN scores on postoperative day 1, day 2 and day 7 after surgery
  - Need for postoperative renal replacement therapy (RRT)
- Sequential Organ Failure Assessment (SOFA) scores on postoperative day 1, day 2 and day 7
- Total fluid volume (crystalloid and colloid)
- Need for rescue therapy
- Postoperative complications within 30 days after surgery: inflammatory response (systemic inflammatory response syndrome or SIRS), infectious (anastomotic leak, surgical site infection, pneumonia, urinary tract infection, sepsis, severe sepsis and septic shock), respiratory (hypoxemia, need for non-invasive or invasive mechanical ventilation, ARDS, pneumonia), neurologic (stroke and postoperative altered consciousness), thromboembolic (deep venous thrombosis, pulmonary embolism), cardiovascular (cardiac arrhythmia, acute heart failure, myocardial infarction), hematologic (thrombocytopenia), renal and surgical (reoperation) complications.

Postoperative renal function will be evaluated with the use of the RIFLE\textsuperscript{20} and AKIN\textsuperscript{21} classification, and on plasma neutrophil gelatinase-associated lipocalin (NGAL) levels. Definitions for postoperative complications are provided in the appendix.

- Duration of ICU and hospital stay
- All-cause mortality at day 30 and 1-yr after surgery
- Blood samples will be collected on day 1, day 2 and day 7 and analyzed for plasma NGAL, creatinine, lactate, C reactive protein, troponin, and amino-terminal pro-brain natriuretic peptide (NT-proBNP)

**Study interventions**

Multicenter, prospective, randomized, stratified, parallel-group clinical trial with concealed allocation to a standard or an individualized treatment strategy:

- **Experimental group**: individualized (preventive) treatment strategy
  - In the individualized treatment group, patients will receive continuous infusion of norepinephrine to maintain SBP within ±10% of the patient resting blood pressure (used as the reference value)

- **Control group**: standard (curative) treatment strategy
  - In the standard treatment group, patients will receive intravenous boluses of ephedrine to treat any drop in SBP below 80 mmHg or lower than 40% from the patient resting blood pressure (used as the reference value)

To help match the two groups and address potential inter-hospital differences, randomization will be stratified per center and according to the urgency of surgery and surgical site (abdominal or non-abdominal surgery).

Decisions about all aspects of patient care during the intraoperative and postoperative periods will be performed according to the expertise of the staff at each center and to routine clinical practice to minimize interference with the trial intervention. Nevertheless, to avoid extremes of clinical practice but also to minimize interference with the trial intervention, study investigators will be strongly encouraged to apply standard measures, as follows:

- Induction of general anesthesia with the use of propofol 2-3 mg/kg, sufentanil 0.2 μg/kg and cis-atracurium 0.15 mg/kg. Inhaled anesthetics will be used for maintenance of general anesthesia, to a target bispectral index between 40 and 60, in addition to intravenous perfusion of sufentanil at 0.1 to 0.2 μg/kg per hour.
- Mechanical ventilation with the use of a tidal volume between 8 and 10 ml/kg predicted body weight, with a positive end-expiratory pressure between 5 and 10 cmH2O, an inspired oxygen fraction (FIO2) to maintain oxygen saturation ≥95% and the respiratory rate adjusted to maintain end-tidal carbon dioxide concentration between 30-35 mmHg.
- Blood transfusion to maintain hemoglobin level at greater than 10 g/dl.
- Core temperature maintained at 37°C.
- Epidural analgesia is authorized for use postoperatively, but not during surgery.
- The following treatments will be prohibited:
  a. Ketamine
  b. Nonsteroidal inflammatory drugs
  c. Benzodiazepine

Angiotensin-converting enzyme inhibitor (ACEI) and angiotensin II receptor antagonist (AIIRA) are routinely withheld the day before surgery. The continuing of ACEI or AIIRA before surgery will be recorded in the case report form.

- Detailed description of all acts performed on patients
  - The day of anesthesia consultation
    All consecutive patients scheduled to undergo abdominal surgery under general anesthesia will be assessed for eligibility.
    During the anesthesia consultation, local investigators will:
    o Verify inclusion and non-inclusion criteria,
    o Invite the patients to participate to the study,
    o Present the study objectives: rationale, benefits and constraints,
    o And provide the study information form
  - Inclusion visit (the day of hospital admission)
    On the day of admission in the surgical unit, the day before surgery, local investigator will:
    o Collect the informed consent form (signed and dated by the patient),
    o Verify inclusion and non-inclusion criteria,
    o Make the randomization, using dedicated, password-protected, SSL-encrypted website and will enter all preoperative data into the electronic web-based case report form (eCRF)
  - Intraoperative period (on arrival in the operating room until discharge)
    Study investigators will be strongly encouraged to apply standard measures to avoid extremes of clinical, as follows:
    - Induction of general anesthesia with the use of propofol 2-3 mg/kg, sufentanil 0.2 μg/kg and cis-atracurium 0.15 mg/kg. Inhaled anesthetics will be used for maintenance of general anesthesia, to a target bispectral index between 40 and 60, in addition to intravenous perfusion of sufentanil at 0.1 to 0.2 μg/kg per hour.
    - Mechanical ventilation with the use of a tidal volume between 8 and 10 ml/kg predicted body weight, with a positive end-expiratory pressure between 5 and 10 cmH2O, an inspired oxygen fraction (FIO2) to maintain oxygen saturation ≥95% and the respiratory rate adjusted to maintain end-tidal carbon dioxide concentration between 30-35 mmHg.
    - Blood transfusion to maintain hemoglobin level at greater than 10 g/dl.
    - Core temperature maintained at 37°C.
In the two study groups, epidural analgesia is authorized for use postoperatively, but not during surgery.

**Trial setting for intraoperative fluid administration and individualized hemodynamic optimization:**
In each group, lactated Ringer’s solution at 4 ml/kg per hour will be used as maintenance fluid during surgery. Additional fluid boluses will be given with the use of an individualized goal-directed therapy protocol aiming to optimize stroke volume index (SVI). In brief, patients will receive 250 ml fluid challenges, within duration of 10 minutes, with a colloid solution (hydroxyethyl starch 130/0.4/6%). Fluid responsiveness is defined as a SVI increase ≥10%. Maximal stroke volume is defined as the absence of a sustained rise in SVI of at least 10% sustained for 20 minutes or more in response to a fluid challenge. No more than 500 ml of fluid will be administered for initial determination of the maximal value of SVI before start of the surgical procedure. Once the maximal value of SVI has been determined after induction of anesthesia, SVI must be maintained throughout the intervention period with subsequent boluses of fluids as required. Further 250 ml fluid challenges should be considered where there is reason to believe the maximal stroke volume may have changed (maximum dose of HES of 30 ml/kg/ per 24hr).

**Trial setting for vasopressor administration:**
During the intraoperative period, vaspressors (ephedrine or norepinephrine) will be administered as follows:

- **Control group (curative treatment of intraoperative arterial hypotension):**
  Patients will receive intravenous ephedrine administered in 6 mg boluses (for a maximum dose of ephedrine not exceeding 60 mg) in case of a drop in SBP below 80 mmHg or lower than 40% from the reference value.

- **Intervention group (individualized preventive treatment of intraoperative arterial hypotension):**
  Patients will receive a continuous infusion of norepinephrine to maintain SBP within ±10% of the reference value. The infusion rate of norepinephrine will be adjusted using a dedicated table (appendix). A single 10 μg/ml concentration of norepinephrine (2.5 mg in 250 ml of 0.9% saline) will be used in the INPRESS trial. The solution of norepinephrine will be prepared in a dedicated syringe by trial personnel, and will be administered through a dedicated peripheral intravenous catheter. Norepinephrine should be initiated during induction of general anesthesia as a continuous infusion at a dose determined according to the patient’s body weight. The dose could then be increased or decreased at the discretion of the attending physician to keep SBP within the target blood pressure. No bolus loading will be used.

**Rescue therapy:** In patients allocated to the control group, if SBP remained below the target value after a maximum dose of 60 mg ephedrine, the use of norepinephrine was permitted as rescue therapy. In patients allocated to the intervention group, a reduction in norepinephrine infusion rate is recommended in case of severe bradycardia (defined as heart rate <40 beats per minute).
- **Postoperative follow-up**
  In each group, the management of patients during the postoperative period will be performed according to each center specific expertise and routine clinical practice. It is suggested to perform postoperative pain management in order to achieve a visual analogue scale (VAS) pain score <3 with the use of paracetamol and nefopam. The use of nonsteroidal inflammatory drugs is prohibited.
  Patients will be assessed at least once a day during hospitalization until hospital discharge and at the time of follow-up evaluation (day 1, day 2, day 7, day 15 and day 30 following surgery).

**Data registration**
Data will be entered into the electronic web-based (Clinsight) case report form (eCRF) by trial or clinical personnel under the supervision of the trial site investigators at each participating center. From the eCRFs the trial database will be established. Paper CRF will be used in case of technical difficulties with the eCRF. Data collection will be monitored by trained research coordinators.

- **Preoperative data (pre-randomization characteristics):**
  - Demographic data (age, sex, weight, height, body mass index)
  - American Society of Anesthesiologists (ASA) physical status
  - Co-morbidities (hypertension Y/N, diabetes Y/N, renal dysfunction Y/N, chronic arterial hypertension Y/N, chronic heart failure Y/N, ischemic heart disease Y/N, diabetes mellitus, Y/N)
  - Use of antihypertensive drugs Y/N
  - Use of angiotensin-converting enzyme inhibitor (ACEI) and/or angiotensin II subtype receptor antagonists (AIIRA) Y/N
  - Use of diuretics Y/N
  - Use of antidiabetics (oral or IV) Y/N
  - Results of blood samples (standard lab. values), including serum creatinine, estimated glomerular filtration rate
  - Digital Symbol Substitution Test (DSST) score
  - Reference (baseline) blood pressure (SBP, DBP)

- **At randomization:**
  - AKI risk index
  - Urgency of surgery (elective, emergency) (stratification variable)
  - Site of surgery (abdominal, non-abdominal) (stratification variable)

- **During the surgical procedure and the 4 hours following surgery:**
  - Date (XX/YY/20ZZ) and hour (XX:YY)
  - Type and doses of hypnotics, opioids and muscle relaxants
  - Values for stroke volume and cardiac index (at 10-min intervals during 1 hr, then every 30 min)
  - Values for SBP, DBP and MBP (at 1-min intervals during the first 10 min after anesthesia induction, then every 10 min)
  - Values for bispectral index
  - Ventilator settings (tidal volume, PEEP, FiO2, RR)
- Type (crystalloids and colloids) and volume (milliliter) of intraoperative fluids
- Blood losses (milliliter)
- Blood transfusion Y/N, number of blood products
- Duration of surgery
- Dose of ephedrine
- Rate (ml/h) of norepinephrine infusion
- Surgical complications Y/N

• Postoperative data (until hospital discharge):
  Patients will be assessed at least once a day during hospitalization until hospital discharge and at the time of follow-up evaluation (day 1, day 2, day 7, day 15 and day 30 following surgery).
  - Postoperative care pathway (surgical ward Y/N, HDU Y/N, and ICU Y/N)
  - Daily lowest values for heart rate, blood pressure, peripheral O2 saturation, respiratory rate, temperature, urine output
  - Variables for SOFA scoring (at day 1, day 2 and day 7)
  - RIFLE and AKIN scores (at day 1, day 2 and day 7)
  - Results of samples of white blood cell, hemoglobin, hematocrit, platelet, prothrombin time, activated partial thromboplastin time, blood-urea nitrogen, creatinine, lactate, CRP, bilirubin, troponin, NGAL, NT-proBNP (standard laboratory values)
  - Postoperative complications (Y/N and date of diagnosis)
  - Unexpected ICU admission Y/N
  - Length of stay in HDU, ICU, and surgical ward
  - Date of hospital discharge
  - Death (Y/N and date)

30 days after surgery:
If the patient is still present in hospital on day 30, follow up will be continued until hospital discharge.
  - Postoperative complications (Y/N and date of diagnosis)
  - Length of stay in HDU, ICU, and surgical ward
  - Date of hospital discharge
  - Death (Y/N and date)

1 year after surgery
  - Survival status (if the patient is deceased, date of death)
Statistics

• Randomization and blinding

After informed consent will be obtained, enrolled patients will be randomized in a 1:1 ratio to either a standard (control group) or an individualized preventive (intervention group) blood pressure treatment strategy by local investigators using a dedicated, password-protected, SSL-encrypted website (CSONline, Clinsight) to allow immediate and concealed allocation. Each patient will be given a unique patient-number and a randomization number. Randomization sequence will be generated by minimization, and will be stratified per center, according to the urgency of surgery (elective or emergency) and according to the surgical site (abdominal or non-abdominal). The participant allocation will be carried out by local investigators who will log into the randomization system using a personal ID code and will enter any relevant information.

It will not be possible to mask the assigned blood pressure treatment strategy from the attending anesthesiologists because they have an ethical responsibility to ensure patient safety until discharge from the operating room. However, procedures will be put in place to minimize the possibility of bias arising because research staff becomes aware of trial group allocation. At each participating center, patients will be followed up for primary and secondary endpoints by members of the research staff who will be unaware of the trial group allocation. At each participating center, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the local principal investigator (PI) or designee who will also be unaware of the trial group allocation.

Moreover, in addition to the aforementioned risk of allocation/selection bias (controlled by randomization) and performance bias, the study protocol will control for the risks of attrition bias (all analyses will be performed on data from the intention-to-treat population), whereas the use of well-defined and pre-specified primary/secondary outcome measures will control for the risk of reporting bias. Finally, the independent trial statistician and the members of the data monitoring and safety committee (DMSC) will also remain blinded for the allocation during analysis.

• Number of patients

Previous data from the literature have shown an overall incidence of SIRS up to 80% following major abdominal surgery.\textsuperscript{23,24} In addition, estimates suggest that between 10% and 40% of patients with SIRS develop severe SIRS,\textsuperscript{10,23} which predisposes surgical patients to adverse outcomes, including respiratory failure, multiple organ dysfunction, sepsis and increased mortality.\textsuperscript{24-26}

Assuming a 40% rate for the primary outcome,\textsuperscript{12} we need to enroll 268 patients (134 patients per group) to have 95% power to detect a 20% effect with respect to the primary outcome, at a two-sided level of 0.05. An interim analysis will be performed at the halfway point (Lan and DeMets method). The steering committee will be responsible to continue, hold or stop the study based on the DMSC recommendations. In order to account for potential withdrawal of consent, the recruitment target is 300 patients.
• **Data analysis: generality**  
  All analyses will be performed with the use of Stata software (version 13, StataCorp, College Station, USA) before the breaking of the randomization code, according to International Conference on Harmonization-Good Clinical Practice guidelines.

Analysis on the primary outcome measure (a composite of SIRS and at least one major organ dysfunction by day 7 after surgery) will be conducted, first, on data from the modified intention-to-treat (ITT) population (defined as all randomized patients, except those who will withdraw consent for the use of their data) and, second, in the per-protocol population (rescue therapy). In addition, each component of the composite primary outcome will be analyzed separately.

Continuous variables will be presented as mean and standard deviations (as median and quartiles, otherwise) and will be compared with the use of the unpaired *t* test or the Mann-Whitney *U* test when appropriate. The Shapiro-Wilk test will be used will be used to assess normality, and the Fisher-Snedecor test to assess homoscedasticity. Categorical data will be presented as exact number and percentage.

A two-sided *P* value of less than 0.05 will be considered for statistical significance of all analyzes.

• **Primary analysis**  
  Data will be analyzed with the use of unadjusted chi-square test (or Fisher's exact test, as appropriate).

• **Secondary analyses**  
  Multiple logistic regression analysis will be used to identify relevant baseline covariates in the intention-to-treat population with anticipated relationship with the primary composite outcome in addition to the stratification variables. Variables tested will be selected if the *P*<0.10 and according to clinical relevance. Adjusted analyses will be performed with the use of robust Poisson generalized-linear-model regression and will be presented as relative risks and 95% confidence intervals. A chi-square test (or Fisher's exact test, as appropriate) will be used for secondary binary outcomes. The Hochberg procedure will be used to adjust for multiple testing of components of the composite primary outcome. Adjusted analyses will be performed with the same adjustment variables. A random-effect model will be used to model longitudinal differences in intraoperative blood pressure between treatment groups, taking into account between and within patient variability. The normality of residuals will be assessed using the Shapiro-Wilk test. Time-to-event curves will be calculated with the use of the Kaplan-Meier method. Results will be expressed as hazard ratios and 95% confidence interval.

• **Method for missing data**  
  If missing data are greater than 5%, an additional analysis will be performed using the multiple imputation method.
• **Statistical analysis**
  Bruno PEREIRA, PhD
  Biostatistic unit, Délégation Recherche Clinique & Innovation (DRCI)
  University of Clermont-Ferrand,
  58, Rue Montalembert, 63003 Clermont-Ferrand cedex
  Clermont-Ferrand, France
  Tel: +33 (0) 473754964 / bpereira@chu-clermontferrand.fr
Safety
Interim analysis of safety will be conducted after enrolment of 50% of patients. The data monitoring and safety committee (DMSC) will provide recommendations about stopping or continuing the trial to the steering committee. All serious adverse, unexpected or possibly related events will be recorded in the CRF and reported to the DMSC.

Responsibilities of the DMSC
The DMSC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The DMSC will provide recommendations about stopping or continuing the trial to the Steering Committee (SC). To contribute to enhancing the integrity of the trial, the DMSC may also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control.

The DMSC will be advisory to the SC. The SC will be responsible for promptly reviewing the DMSC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The DMSC is an independent multidisciplinary group, consisting of clinicians and a biostatistician, that collectively has specific expertise in the management of surgical patients, and in the conduct, monitoring and analysis of randomized clinical trials:
- Catherine Paugam-Burtz, MD, PhD (Dept. of Anesthesiology and Critical Care Medicine, Beaujon Hospital, Assistance Publique-Hôpitaux de Paris (AP-HP), Clichy, France)
- Karim Asehnoune, MD, PhD (Dept. of Anesthesiology and Critical Care Medicine, Hotel Dieu, University Hospital of Nantes, Nantes, France)
- Nicolas Molinari, PhD (Department of Statistics, Lapeyronie Hospital, University Hospital of Montpellier, Montpellier, France)

Right of access to source document and data
- Access to data
  The sponsor is responsible for obtaining the agreement of all parties involved in the research in order to guarantee direct access to all study sites, source data, source documents and reports for purposes of the sponsor’s quality control and audit.

  The investigators will provide access to the documents and individual data that are strictly necessary for purposes of monitoring, quality control and audit of the biomedical research, to the persons authorized to consult said documents pursuant to the legislative and regulatory provisions in force (articles L.1121-3 and R.5121-13 Public Health Code).

- Source data
  Source documents, defined as any original document or object which proves the existence or accuracy of data or information recorded during the clinical study, will be
stored for a period of 15 years by the investigator or by the hospital in the case of a hospital medical record.

- **Data confidentiality**
  Subject to the provisions relating to the confidentiality of data to which persons in charge of quality control of biomedical research have access (article L.1121-3 Public Health Code), and subject to the provisions relating to the confidentiality of information as concerns in particular the nature of the products being studied, the trials, the persons undergoing the research and the results obtained (article R.5121-13 Public Health Code), persons having direct access shall take all necessary precautions to ensure the confidentiality of the information relating to the products being studied, the trials, the persons undergoing the research and notably their identity, and the results obtained.

  These persons, as well as the investigators themselves, are bound by professional secrecy (in accordance with the conditions laid down in articles 226-13 and 226-14 of the penal code).

  During the biomedical research or upon its completion, the data collected on the research subjects and transmitted to the sponsor by the investigators (or any other specialized study staff) shall be rendered anonymous.

  In no case shall the names or addresses of the persons undergoing the research appear.

  Anonymity of the subjects will be guaranteed by the creation of a subject identifying number.

  The sponsor will ensure that each research subject has given his written consent allowing access.

**Quality control and assurance**

- **Engagement of the investigators and the sponsor of the study**
  The investigator undertakes to conduct the study in compliance with public health law 2004-806 of 9 August 2004 relating to biomedical research, the implementing decree 2006-477 of 26/04/2006 amending chapter 1 of title II of book 1 of the first part of the Public Health Code relating to biomedical research, and with the bylaws in force. The study will also be conducted in compliance with Good Clinical Practices for biomedical research on medicinal products for human use, as laid down in article L.1121-3 Public Health Code and the decree of 24 November 2006.

  The investigator also undertakes to comply with the Declaration of Helsinki of the World Medical Assembly (Tokyo 2004, revision).

- **Quality assurance**
  Clinical Research Associates (CRAs) designated by the sponsor will ensure the proper conduct of the study, the collection of data generated in writing, and their documentation, recording and reporting, as per the Standard Operating Procedures in effect at the Clermont-Ferrand University Hospital and in compliance with Good Clinical Practices and legislative and regulatory provisions in force.
• **Quality control**
  The investigator guarantees the authenticity of the data collected during the study and accepts the legal provisions authorizing the study sponsor to implement quality control.
  The coordinating investigator and associated investigators therefore agree to make themselves available during Quality Control visits by the Clinical Research Associate that will be scheduled at regular intervals. The following items will be examined at each visit:
  - Informed consent
  - Compliance with the study protocol and procedures
  - Quality of data recorded in the case report forms: accuracy, missing data, coherence with source documents (medical records, appointment calendars, original copies of laboratory results, etc.)
  - Management of any study products.

• **Case report form**
  At each participating center, data will be collected and entered into a dedicated, password-protected, SSL-encrypted electronic web-based case report form (eCRF) by trial or clinical trained personal, blinded to the allocation group, under the supervision of the trial site investigators.

**Ethical considerations**

• **Ethics Committee**
  The study protocol, patient information notice and consent form will be submitted to the Comité de Protection des Personnes Sud Est VI.
  Notification of a favorable opinion from the Ethics Committee will be transmitted to the sponsor and to ANSM. The sponsor of the study will send an authorization request to ANSM prior to study start.

• **Information for patients and written informed consent form**
  Patients will be informed in complete and faithful terms and in understandable language of the objectives and constraints of the study, the potential risks, the required observation and safety measures, and their right to refuse to participate in the study or to revoke their consent at any time. The investigator must also inform the subjects of the Ethics Committee opinion.
  All information appears in an information notice and consent form given to the patient. Written informed consent will be obtained by the investigator. These documents will be approved by the competent Ethics Committee.
  Two original copies will be co-signed by both the investigator and the patient and the parents. The second copy is to be kept in the patient’s medical record.

• **Protocol amendments**
  Protocol amendments must be qualified as substantial or non-substantial. According to their nature, they will be the object of a new Ethics Committee opinion and/or authorization from the competent authority.
Data processing and storage of study documents

- **Data entry and processing**
  At each participating center, data will be collected and entered into the electronic web-based case report form (eCRF) by trial or clinical trained personal (clinical research associate), blinded to the allocation group, under the supervision of the trial site investigators.
  Data analysis will be carried out at the biostatistical unit, Regional Clinical Research Delegation (DRCI), University of Clermont-Ferrand.

- **CNIL**
  This study enters within the scope of “Reference Methodology” (MR-001) in application of the provisions of the law of 6 August 2004 relating to the protection of natural persons with regard to the processing of personal data and amending the law of 6 January 1978 relating to computer processing, data files and civil liberties. This change was approved by decision of 5 January 2006. The University Hospital of Clermont-Ferrand, which sponsored the study, has signed a commitment to comply with this “Reference Methodology” on 15/03/2007.

- **Data retention and archiving**
  The following documents will be archived under the study name in the Department of Anesthesiology and Critical Care Medicine (Prof. Jean-Etienne Bazin, Head of department, Estaing University Hospital, Clermont-Ferrand, France) until the end of the period of practical usefulness (36 months, including inclusion of patients and data analysis).
  These documents are:
  - Protocol and appendices, and any amendments,
  - Signed, original information notices and consent forms,
  - Individual data (authenticated copies of raw data),
  - Follow-up documents
  - Statistical analyses
  - Final study report
  At the end of the period of practical usefulness, all documents to be archived, such as defined in procedure PG.06.005 “Management of documentation relating to protocols” of Clermont-Ferrand Hospital will be transferred to the central archives and placed under the sponsor’s responsibility for a period of 15 years after study completion, in accordance with institutional practices.
  These documents cannot be moved or destroyed without the sponsor’s permission. After the 15 years are up, the sponsor will be consulted for destruction. All the data as well as all documents and reports may be subject to audit or inspection.

**Funding and insurance**
In accordance with regulatory provisions, Clermont-Ferrand Hospital, in its capacity as sponsor, has taken out civil liability insurance covering any damages resulting from the research with the Société Hospitalière d’Assurances Mutuelles (SHAM).

It should be noted that non-observance of the legal conditions of the research (absence of Ethics Committee opinion, absence of ANSM authorization, non-consent of subjects, continuation of a suspended or prohibited study) shall render this coverage void.
**Communication - Rules for publication**

The Steering Committee will grant authorship depending on personal involvement according to the Vancouver definitions. The listing of authors will be as follows: E Futier (principal investigator) will be responsible for the writing of the manuscript and will be the first author, and the next authors will be the other members of the Steering Committee according to the number of included patients per study site, then trial site investigators dependent on the number of included patients per site, S Jaber will appear as the last author and then ‘for the INPRESS study group’.

Funding sources will have no influence on data handling or analysis or writing of the manuscript. Side studies will be allowed if supported by the Steering committee.

The study will be registered and declared at ClinicalTrials.gov.
References


Appendix 1

Acute Kidney Injury (AKI) risk index
(Kheterpal S et al. Anesthesiology 2009; 110(3):505-515)

The acute kidney injury (AKI) risk index ranges from 1 to 5 classes, with higher classes indicating a higher risk of postoperative kidney injury.

The AKI risk index is composed of 9 independent preoperative risk factors:
1. Age ≥56 years
2. Male sex
3. Congestive heart failure
4. Chronic hypertension
5. Emergency surgery
6. Abdominal surgery
7. Ascites
8. Renal insufficiency-mild or moderate (preoperative serum creatinine value >1.2 mg/dl or >105.6 µmol/l)
9. Diabetes mellitus-oral or insulin therapy

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class I</td>
<td>zero, one, or two risk factors</td>
</tr>
<tr>
<td>Class II</td>
<td>three risk factors</td>
</tr>
<tr>
<td>Class III</td>
<td>four risk factors</td>
</tr>
<tr>
<td>Class IV</td>
<td>five risk factors</td>
</tr>
<tr>
<td>Class V</td>
<td>six or more risk factors</td>
</tr>
</tbody>
</table>
Appendix 2
RIFLE and AKIN classifications
(Bellomo R et al. Crit Care 2004;8:R204-12

Risk, Injury, Failure, Loss, End-stage (RIFLE) kidney disease classification

<table>
<thead>
<tr>
<th>Class</th>
<th>Glomerular Filtration Rate criteria</th>
<th>Urine output criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk</td>
<td>Serum creatinine increase × 1.5</td>
<td>&lt;0.5 ml/kg/h × 6h</td>
</tr>
<tr>
<td>Injury</td>
<td>Serum creatinine increase × 2</td>
<td>&lt;0.5 ml/kg/h × 12h</td>
</tr>
<tr>
<td>Failure</td>
<td>Serum creatinine increase × 3, or serum creatinine ≥4 mg/dl (with an acute rise &gt;0.5 mg/dl)</td>
<td>&lt;0.3 ml/kg/h × 24h, or anuria × 12h</td>
</tr>
<tr>
<td>Loss</td>
<td>Persistent acute renal failure = complete loss of kidney function</td>
<td></td>
</tr>
<tr>
<td>End-stage kidney disease</td>
<td>End-stage kidney disease &gt;3 months</td>
<td></td>
</tr>
</tbody>
</table>

To convert the values for serum creatinine from milligram per deciliter to micromoles per liter, multiply by 88.4.

Acute Kidney Injury Network (AKIN)

<table>
<thead>
<tr>
<th>Stage</th>
<th>Creatinine</th>
<th>Urine output</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Creatinine increase × 1.5</td>
<td>&lt;0.5 ml/kg/h × 6h</td>
</tr>
<tr>
<td>2</td>
<td>Creatinine increase × 2</td>
<td>&lt;0.5 ml/kg/h × 12h</td>
</tr>
<tr>
<td>3</td>
<td>Creatinine increase × 3</td>
<td>&lt;0.3 ml/kg/h × 24h</td>
</tr>
</tbody>
</table>
Appendix 3
Definitions for postoperative complications

Criteria for Systemic Inflammatory Response Syndrome (SIRS)\textsuperscript{27}

SIRS is defined by two or more of the following:

1. Core temperature >38°C or <36°C. (Core temperature was rectal or tympanic). If oral, inguinal or axillary temperatures were used, 0.5°C were added to the measured value.
2. Heart rate >90/min. If patient had an atrial arrhythmia, record the ventricular rate. If patients have a known medical condition or are receiving treatment that would prevent tachycardia (for example, heart block or beta blockers), they must meet two of the remaining three SIRS criteria.
3. Respiratory rate > 20/min or a PaCO\textsubscript{2} <32 mmHg (4.3 kPa) or mechanical ventilation for an acute process.
4. White Blood Cell (WBC) count of >12 x 10\textsuperscript{9}/l or <4 x 10\textsuperscript{9}/l.

SIRS score\textsuperscript{24}
The magnitude of the inflammatory response attributable of surgery or surgical stress is evaluated using the SIRS score, ranging from 0 to 4 (1 point for each parameter) with the highest score indicating more severe inflammatory response.

Sepsis, severe sepsis and septic shock criteria\textsuperscript{28}

Sepsis is defined as:

1. Defined focus of infection and
2. At least two systemic inflammatory response syndrome (SIRS) criteria.
   Defined focus of infection is indicated by either an organism grown in blood or sterile site, or an abscess or infected tissue (e.g. pneumonia, peritonitis, urinary tract, vascular line infection, soft tissue, etc.).

Severe sepsis is defined by sepsis plus at least one organ failure, hypotension or hypoperfusion. Septic shock was sepsis-induced hypotension despite adequate fluid resuscitation along with the presence of perfusion abnormalities.

Criteria for surgical site infection (SSI)
Surgical infection site within 30 days after the operative procedure is defined according to the criteria of the Centers for Disease Control and Prevention (CDC).\textsuperscript{29}
Sequential Organ Failure Assessment (SOFA) score\(^{30}\)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Score</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Respiration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PaO(_2)/FiO(_2) mmHg</td>
<td>≥400</td>
<td>&lt;400</td>
<td>&lt;300</td>
<td>&lt;200</td>
<td>&lt;100 with respiratory support</td>
<td></td>
</tr>
<tr>
<td><strong>Coagulation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets, (×10^{3}/\text{mm}^3)</td>
<td>≥150</td>
<td>&lt;150</td>
<td>&lt;100</td>
<td>&lt;50</td>
<td>&lt;20</td>
<td></td>
</tr>
<tr>
<td><strong>Liver</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilirubin µmol/l</td>
<td>&lt;20</td>
<td>20–32</td>
<td>33–101</td>
<td>102–204</td>
<td>&gt;204</td>
<td></td>
</tr>
<tr>
<td><strong>Cardiovascular</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>MAP ≥70 mmHg</td>
<td>MAP &lt;70 mmHg</td>
<td>dopamine ≤5.0 (µg/kg/min) or any dose dobutamine</td>
<td>dopamine &gt;5.0 (µg/kg/min) or noradrenaline ≤0.1</td>
<td>dopamine &gt;15.0 (µg/kg/min) or adrenaline &gt;0.1 or noradrenaline &gt;0.1</td>
<td></td>
</tr>
<tr>
<td><strong>Central nervous system</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glasgow Coma Scale score</td>
<td>15</td>
<td>13–14</td>
<td>10–12</td>
<td>6–9</td>
<td>&lt;6</td>
<td></td>
</tr>
<tr>
<td><strong>Renal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, µmol/l</td>
<td>&lt;110</td>
<td>110–170</td>
<td>171–299</td>
<td>300–440</td>
<td>&gt;440</td>
<td></td>
</tr>
<tr>
<td>Urine output</td>
<td>&lt;500 ml/day</td>
<td>&lt;200 ml/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Criteria for postoperative pulmonary complications
1. **Criteria for postoperative hypoxemia:**
   Hypoxemia is defined as a PaO\(_2\) <60 mmHg or SpO\(_2\) <90% on room air
2. **Criteria for noninvasive ventilation:**
   Noninvasive ventilation will be considered in case of presence and persistence for more than 30 minutes of hypoxemia (as defined above) and at least one of the following:
   a) A respiratory rate higher than 30/min
   b) Clinical signs suggestive of intense respiratory muscle work and/or labored breathing, such as use of accessory respiratory muscles, paradoxical motion of the abdomen, or intercostal retraction
3. **Criteria for acute respiratory distress syndrome (ARDS):**
   ARDS was defined according to the American–European Consensus Conference criteria\(^{31}\)
4. **Criteria for postoperative pneumonia:**
   Pneumonia is suspected upon the presence of new and/or progressive pulmonary infiltrates on chest radiograph plus two or more of the following criteria:
   a) Fever ≥38.5°C or hypothermia <36°C
   b) Leukocytosis ≥12000 WBC/mm\(^3\) or leukopenia <4000 WBC/mm\(^3\)

Criteria for postoperative altered consciousness
The presence of postoperative altered consciousness by day 7 after surgery will be determined clinically by the treating physician, and defined as a Glasgow Coma Scale (GCS) score of 14 or less (SOFA sub-score of 1 point or more in the neurologic
component). Additionally, whenever possible, the Digital Symbol Substitution Test (DSST) score will be recorded.
Appendix 4
Trial setting for norepinephrine administration

Single concentration: 10 µg/ml norepinephrine (add 2.5 mg of norepinephrine into 250 ml 0.9% NaCl).

The infusion rate of norepinephrine is based on patient's body weight:

<table>
<thead>
<tr>
<th>Norepinephrine µg/kg/min</th>
<th>50</th>
<th>55</th>
<th>60</th>
<th>65</th>
<th>70</th>
<th>75</th>
<th>80</th>
<th>85</th>
<th>90</th>
<th>95</th>
<th>100</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>6</td>
<td>6.6</td>
<td>7.2</td>
<td>7.8</td>
<td>8.4</td>
<td>9</td>
<td>9.6</td>
<td>10.2</td>
<td>10.8</td>
<td>11.4</td>
<td>12</td>
</tr>
<tr>
<td>0.03</td>
<td>9</td>
<td>9.9</td>
<td>10.8</td>
<td>11.7</td>
<td>12.6</td>
<td>13.5</td>
<td>14.4</td>
<td>15.3</td>
<td>16.2</td>
<td>17.1</td>
<td>18</td>
</tr>
<tr>
<td>0.04</td>
<td>12</td>
<td>13.2</td>
<td>14.4</td>
<td>15.6</td>
<td>16.8</td>
<td>18</td>
<td>19.2</td>
<td>20.4</td>
<td>21.6</td>
<td>22.8</td>
<td>24</td>
</tr>
<tr>
<td>0.05</td>
<td>15</td>
<td>16.5</td>
<td>18</td>
<td>19.5</td>
<td>21</td>
<td>22.5</td>
<td>24</td>
<td>25.5</td>
<td>27</td>
<td>28.5</td>
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