Cleveland Clinic

Hemodynamic Effect of Norepinephrine Versus Vasopressin on the Pulmonary Circulation in Cardiac Surgery Patients: a Comparative-effectiveness Pragmatic Trial

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Background:

Cardiopulmonary bypass (CPB) during cardiac surgery is well known to activate a variety of neurohormonal and endocrine reactions in human body that disrupt the balance of systemic vasculature tone and organ perfusion, which ultimately lead to vasoplegic shock requiring administration of vasopressors. Several vasopressors targeting different receptors are available, and often required to maintain adequate perfusion pressure after CPB in cardiac surgery. These are phenylephrine (alpha-adrenoreceptor agonist), norepinephrine (NE, alpha- and beta-adrenoreceptor agonist), vasopressin (VP, V1 receptor agonist) and angiotensin II (AT1 receptor agonist). Both NE and VP are acceptable first choice agents for treatment of post-CPB vasoplegic shock, and the selection between the two agents is mostly dependent on the preference of individual anesthesiologists.

Most of the literature on the effects of NE versus VP on pulmonary vasculature is based on *in vitro* studies, which demonstrated that in contrast to NE, VP does not cause vasoconstriction in animal and human pulmonary artery segments.[1-4] Interestingly, VP may even cause vasodilation in pulmonary vasculature under hypoxic conditions through an endothelial V1 receptor mediated nitric oxide production, which relaxes the underlying vascular smooth muscle.[5] An *in vivo* experiment using anesthetized and ventilated porcine models showed that VP maintained pulmonary artery pressure (PAP) and decreased pulmonary vascular resistance (PVR)/systemic vascular resistance (SVR) ratio by 45%, while NE increased PAP and PVR/SVR ratio,[6] also suggesting more favourable effect of VP on pulmonary vasculature.

Clinical evidence regarding NE versus VP effects on pulmonary vasculature during cardiac surgery is limited and unclear. In a recent large (n=300) randomized controlled trial (RCT), Hajjer et al focused on NE versus VP use in patients with vasoplegic shock after cardiac surgery, and found that VP group had lower mortality or severe complications including stroke, prolonged mechanical ventilation, deep wound infection, reoperation or acute renal failure, with unadjusted hazard ration (HR) of 0.55 (95% CI, 0.38 to 0.80; P = 0.0014).[7] However, the study did not report pulmonary or systemic arterial pressures, and the influences of NE versus VP on pulmonary vasculature and right ventricular (RV) function remains unclear. A small (n=20) RCT found that both NE and VP increased PAP in patients having coronary artery bypass grafting (CABG) surgery.[8] A retrospective analysis demonstrated that addition of VP to NE decreased PAP in patients having catecholamine resistant septic shock and post-cardiotomy shock.[9] However, a concomitant decrease in the cardiac output in patients who received VP, may explain the decrease in PAP, rather than direct effect on the pulmonary vasculature.

Pulmonary arterial hypertension (PAH) is defined as resting mean PAP > 20 mmHg and pulmonary capillary wedge pressure (PCWP) < 15 mmHg.[10] Increased PAP causes RV pressure overload, which might lead to RV failure through multiple mechanisms including but not limited to: a) decreased aorta-RV pressure gradient reduces epicardial systolic flow and thus right coronary artery (RCA) perfusion;[11] b) RV's limited contractile reserve, despite dilatation or hypertrophy as compensation, limits its capacity of adaptation to an increased afterload;[12] c) beta-adrenoreceptor desensitization and downregulation.[13] As RV failure requiring intensive care unit admission and inotropic support has an extremely high inpatient mortality rate of > 45%,[14] monitoring RV function, and choice of a vasopressor with minimal effect on PAP and thus RV function would be important and beneficial.

Clinically it remains unclear, if NE and VP have different effect on PAP per same unit increase in mean arterial pressure (mPAP-to-MAP) in patients undergoing cardiac surgery. It also is unclear, if the two agents exert different effect in patients who have normal PAP, versus those who have pulmonary arterial hypertension.

The specific aims of our study are to compare 1) the relative increase in the mPAP with the same unit increase in MAP and 2) RV function assessed by global longitudinal strain (GLS), between VP and NE in patients with normal and increased pulmonary artery pressure, who require vasopressor support during cardiac surgery. We hypothesize that the use of vasopressin compared with norepinephrine induces a lower mPAP-to-MAP ratio, in cardiac surgical patients with and without pulmonary hypertension. Second, we will test the hypothesis that vasopressin is associated with improved right ventricular global longitudinal strain compared to norepinephrine in patients requiring vasopressor support during cardiac surgery.

Study Design:

This unblinded alternating trial will compare the effect of NE versus VP on mPAP-to-MAP ratio in patients having cardiac surgery. The treatment will be randomized in one week blocks and not by patient, using the RedCap system. This means that during any week, eligible patients will be exposed to the same vasopressor agent,. And the following week there will be new randomization in place. Allocations will be directly communicated to anesthesia personnel and by signs prominently displayed in anesthesia ready room.

Inclusion Criteria:

1. Adults> 18 years of age
2. Elective cardiac surgery with the use of CPB
3. Patients with pulmonary artery catheter insertion
4. Systemic hypotension (MAP < 70 mmHg) requiring continuous infusion of vasopressor

Exclusion Criteria:

1. Transplant surgery
2. Ventricular assist device implantation other than intraaortic balloon counterpulsation
3. Pulmonary endarterectomy
4. Thoracoabdominal aneurysm repair
5. Use of extracorporeal life support (ECMO) before or after CPB

6. Inhalational pulmonary vasodilators (e.g. Epoprostenol) administration before insertion of pulmonary artery catheter
7. Vasopressin is started as the first choice of pressor per clinical staff discretion

Informed Consent Waver:

We request waiver of informed consent for two reasons. The first is, there are similar indications for treatment and clinical efficacy of the two agents, which minimizes the risks associated with the study protocol: 1) both norepinephrine and vasopressin are considered acceptable and equally efficacious intial treatments for hypotension during cardiac surgery, and both are used routinely at the Cleveland Clinic; 2) the study is unblinded. The clinicians are aware of the vasopressor they administer, and completely at liberty to ignore the protocol-proposed vasopressor in any patient likely to benefit from an alternative approach. The second reason we request waived consent is that the proposed trial would be impractical with conventional consent[15]: 1) we cannot predict which patients will have a pulmonary artery catheter inserted for the surgery, a decision that is made when the attending surgeon and anesthesiologist "huddle" (standard procedure to review and discuss perioperative details and plan for the surgical case) just before anesthetic induction; and, 2) we cannot predict which patients will develop severe hypotension after CPB and require vasopressor support. As an alternative to the conventional consent, we provide a patient information letter, which describes the study protocol and provides information regarding the two vasopressors. It will be included in the preoperative cardiac surgery package for patients seen at the "To Come In" Clinic (the preoperative clinic for cardiac surgery) or during their hospital stay if they are admitted to the hospital before surgery. We provide an option to opt out from participation in the study Investigators contact information has been provided in the information letter, and when a patient opted out from participation, the investigators will contact the anesthesiologist providing care for this patient to inform them that the patient will not be included in the study. A separate file will contain the records of all patients who refused participation in the study, and they will not be included in the analysis.

Outcomes:

Primary outcome:

We will compare the mPAP-to-MAP ratio between patients who received norepinephrine versus vasopressin during the post-intervention period. **Post intervention** hemodynamic measurements will be recorded at the end of surgery in the period between chest closure and last stitch. If this time point is unavailable, we will take the first 15 of the last 20 minutes in the operating room marked by "transport to recovery" *(The last 5 min are not considered, because this involves patient transfer to the ICU bed which can affect the hemodynamic measurements*).

Secondary outcome:

Compare GLS between patients who received norepinephrine versus vasopressin intraoperatively. Post intervention measurements will be recorded in the period after chest closure to last stitch. If this time point is unavailable, we will take the the first 15 of the last 20 minutes in the operating room marked by "transport to recovery".

Exploratory endpoints:

1. Cardiac index –after PA catheter placement, and after chest closure
2. Peak creatinine level within 72 hours after surgery
3. Atrial fibrillation within 72 hours after surgery
4. Duration of hospitalization
5. Incidence of stroke
6. Prolonged mechanical ventilation > 72 hours
7. Hospital mortality
8. Renal replacement therapy
9. Need for reoperation
10. Duration of inotropic support
11. Duration of vasopressor support
12. Post-intervention central venous pressure
13. Bowel ischemia – diagnosed with imaging and requiring intervention
14. Lactate level – peak lactate level in the first 48 hours postoperatively
15. Tricuspid annulal plane excursion – TEE variable after chest closure
16. Fractional area of change – TEE variable after chest closure

Standard Anesthesia Procedures

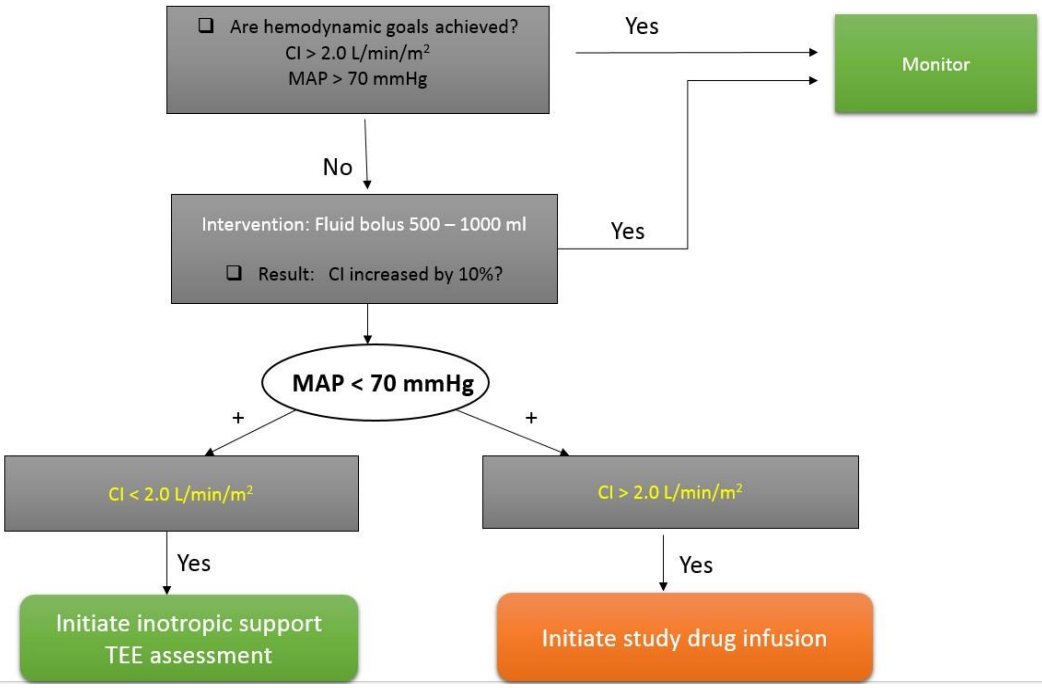
At our institution, cardiac surgical patients are monitored with standard ASA monitors, pre-induction brachial arterial line, and central venous cannula, most commonly placed in the internal jugular vein post-induction. Pulmonary artery catheters are routinely placed in patients with any of the following: preexisting pulmonary hypertension, reduced left or right ventricular systolic function, multi-redo surgeries, complex aortic procedures, and other complex cardiac surgeries. Routinely used induction medications include midazolam, fentanyl, lidocaine, propofol, etomidate, and rocuronium, although specific drugs used depends on the individual patient's medical condition and the preference of the staff anesthesiologist. Maintenance of anesthesia is with inhaled isoflurane. We maintain ventilation using tidal volumes 6-8cc/kg and PEEP 5-10 cmH_2O with ventilation adjusted to maintain normal pH. At the end of surgery, patients are typically transported to the ICU intubated on an intravenous infusion of propofol.

Study Drug Preparation and Administration:

The study medications norepinephrine and vasopressin will be supplied in the operating room in one-week intervals. Norepinephrine is stored in pre-mixed bags (4mg/250ml) in the OR main pixys machine, where it is readily available for use. Vasopressin is stored in each OR pixys machine, in 20 U/1ml vials, which are mixed in 100cc bags of dextrose 5% solution. Both medications are infused through a medication pump (SmartPump) and infused through the medication port of the pulmonary artery catheter. The clinician enters the desired dose for norepinephrine (mcg/min), and for vasopressin (U/min). All clinical staff participating in patient's care will be unblinded to the treatment.

Initiation of the study medication will be at the discretion of the staff anesthesiologist when there is need for vasopressor support while MAP < 70 mmHg, only after volume status has been optimized in the presence of cardiac index > 2.0 L/min/m^2 (hemodynamic management protocol - figure 1).
If the vasopressor needs to be started in the process of separation from CPB, there are no definitive hemodynamic criteria to guide its initiation. Thus, it would be entirely per anesthesiologist discretion.

Hemodynamic protocol for management of intraoperative hypotension (MAP < 70 mmHg)



The study medication administration will be titrated from lowest to highest dose in a step wise fashion every 3-4 min. NE doses range from 2 to 18 µg/min, and VP doses from 0.01 to 0.06 U/min (Table 1)[16,17,18]. The goal is to return systemic MAP to 70 mmHg and sustain that pressure. If the study medication of the week is titrated to its maximum infusion rate and the blood pressure goal is not achieved, the opposite vasopressor can be added, as a second agent. In other words, if the study drug is norepinephrine, then the second agent will be vasopressin. If the blood pressure target is exceeded, the second agent is tapered down first, and then the primary study medication dose is decreased if necessary. Prior to reaching the maximum dose, and during the drug titration, if acute elevation of MAP is needed, boluses of norepinephrine can be administered. This practical approach to vasopressor administration and titration described in our protocol is consistent with the current clinical management of hypotension during cardiac surgery at the Cleveland Clinic.
Study medication will be considered discontinued when it is no longer required because MAP is at goal. If at the end of the case, the patient still requires vasopressor support, the known study medication will be continued at the current dose, which provides stable vital signs.

Drug titration table based on equipotency drug properties

Norepinephrine (mcg/min)	Vasopressin (Units/min)
2	0.01
4	0.015
6	0.02
8	0.03
10	0.035
12	0.04
15	0.05
18	0.06

Data Collection:

Patient data will be collected prospectively and stored in RedCap database. Hemodynamic and echocardiographic parameters will be recorded after pulmonary artery catheter insertion; *postintervention period* is the interval between chest closure and last stitch. If this timepoint is unavailable in the anesthesia record, we will take the first 15 of the last 20 minutes before patient transport from the OR to the ICU. The parameters that will be recorded are as following:

1. time weighted average systolic, mean, diastolic pulmonary arterial pressures from ARKS
2. time weighted average systolic, mean, diastolic systemic arterial pressures from ARKS
3. time weighted average central venous pressure
4. Cardiac output/cardiac index by thermodilution – the recorded measurement is the average value from 3 consecutive measurements, provided the difference between the measurements in no more than 10%. – by the clinician
5. Right ventricular global longitudinal strain – from intraoperative transesophageal echocardiography midesophageal 4 chamber view. The images will be obtained in the operating rooms by the anesthesiologist providing patient care with Phillips or GE echo machines. The right ventricular strain will be measured off line using Syngo Velocity Vector Imaging (VVI) by Siemens Healthineers Global.

The infusion rate of the study medications, as well as other medications, such as inotropic agents, insulin, inhaled epoprostenol, antifibrinolytic agents, etc, on continuous infusion will be recorded in ARKS.

We will report the following patient demographic and clinical parameters:

I. Demographic information
    1. Age
    2. Sex

3. Body Mass Index

II. Preoperative comorbid conditions
1. Hypertension
2. Coronary artery disease
3. Diabetes
4. Chronic kidney disease
5. Peripheral artery disease
6. History of stroke/cerebral vascular incident
7. Congestive heart failure
8. Preoperative left ventricular ejection fraction
9. Smoking
10. Hyperlipidemia
11. Chronic obstructive pulmonary disease
12. Type of surgery – isolated valve, isolated coronary artery bypass, combined bypass and valve surgery, major aortic surgery
13. Preexisting right ventricular dysfunction
14. Preexisting pulmonary hypertension
15. Calculated EuroSCORE (European System for Cardiac Operative Risk Evaluation)

III. Intraoperative variables
1. Primary or repeat open heart surgery
2. Blood transfusions – units of red blood cell concentrates, fresh frozen plasma, platelet concentrates, cryoprecipitate
3. Inotropic and vasopressor requirements – continuous infusions at the end of surgery (epinephrine in mcg/min; norepinephrine in mcg/min; vasopressin IU/min; milrinone mcg/kg/min)
4. Duration of surgery (minutes)
5. Duration of CPB (minutes)
6. Duration of aortic cross clamp time
7. Total amount of crystalloid (Lactated Ringer's and Normal Saline collectively) and albumin 5% - in milliliters
8. Milrinone infusion after separation from CPB – mcg/kg/min at the end of the case
9. pH value (from last intraoperative blood gas analysis in anesthesia record
10. Epinephrine infusion – mcg/min at the end of case
11. Cardiac output/cardiac index – after PA catheter placement and post intervention
12. Epoprostenol inhalational infusion post CPB
13. Use of rescue vasopressor agents – hydroxocobalamine; methylen blue
14. Pulmonary artery wedge pressure after chest closure (PCWP) derived from the pulmonary artery catheter
15. Pulmonary vasular resistance calculated value (PAPm – PCWP)/cardiac output

IV. Echocardiographic variables
1. Global right ventricular longitudinal strain
2. Amount of mitral regurgitation pre-CPB and post CPB

Statistical Analysis

Control for potential confounding variables

Baseline variables will be summarized via standard summary statistics and balance on the baseline variables across patients given norepinephrine versus vasopressin will be assessed using standardized difference (differences in means or proportions divided by pooled standard deviation). Since vasopressor assignment is carried by week instead of by randomizing patients, baseline variables will be controlled for using inverse probability of treatment weighting (IPTW). The propensity score for each patient will be calculated using covariate balancing propensity score algorithm and the weight for each patient will be calculated as the inverse of propensity score if in the norepinephrine group and the inverse of (1 – propensity score) if in the vasopressin group. Balance on the baseline variables will be assessed again after weighting and variables with ASD > 0.10 will be considered as imbalanced and adjusted for in the models below.

Main Analysis

We will include a *per protocol* analysis and an *intention to treat* analysis. The *per protocol* analysis will be primary. The *per protocol* analysis will include all patients who receive the study drug at the end of the case during the post-intervention measurement period. The *intention to treat* analysis will be secondary and will include all patients who received the study drug, but the study drug was discontinued before the post-intervention period.

For the primary analysis, we will compare mPAP-to-MAP ratio between chest closure and last stitch, in patients who received norepinephrine versus vasopressin through a linear mixed model, with individual patients weighted as described above. We will incorporate a random intercept for each week to account for intra-week correlation and potential correlation between weeks over time. Normality of mPAP-to-MAP relative change will be tested and if the distribution is found to be not normal, proper transformation will be performed before fitting the relative increase into the model. Interaction between treatment and baseline mPAP-to-MAP will be assessed at a significance level of 0.10 to see if the treatment effect is associated with baseline mPAP-to-MAP. For the secondary analysis, right ventricular global longitudinal strain will be compared through a linear regression model with patients weighed according to IPTW.

For the exploratory analysis, cardiac Index and creatinine level will be compared using linear mixed models, incorporating a random intercept for each week. Duration of inotropic/vasopressor support and duration of hospitalization will be log-transformed to meet the normality assumption and then compared using linear mixed models, properly adjusting for intra-class correlation as described above. Other binary variables will be compared using a generalized linear mixed model with logit link, properly adjusting for intra-class correlation as described above. For all the comparison on the exploratory variables, patients will be weighted according to IPTW to adjust for baseline variables. As these results are exploratory, the Bonferroni correction will NOT be used to adjust significance levels.

Interim Analysis

Because of the small sample size required, we will perform only one interim at 50% of the planned maximum enrollment to assess for efficacy and futility using a group sequential design with gamma spending functions using gamma of -4 for efficacy and -1 for futility. We will stop the trial and conclude efficacy if P-value on the first interim is smaller than 0.0298, or conclude futility if P-value on the first interim is greater than 0.27.

Subgroup and Sensitivity Analyses

1. For the primary and secondary outcomes, we will perform a subgroup analysis to assess treatment effect in patients with pre-existing significant pulmonary hypertension (defined as mean PAP >40 mmHg after pulmonary artery catheter placement vs. patient without (mean PAP <40 mmHg). The subgroup analysis will be performed by adding treatment-group interaction term into the regression models. Interaction terms will be tested at a significance level of 0.10, and regardless of the significance of the interaction terms, treatment effect will be reported separately by the subgroups.

2. As Inhaled or intravenous pulmonary arterial vasodilators including milrinone or epoprostenolol will affect post-CPB pulmonary artery pressures, we will perform a sensitivity analysis that excludes patients who receive milrinone or epoprostenolol post CPB.

Sample size calculation:

Based on the data query for a sample of 732 patients from 2018, mPAP-to- MAP ratio has a mean ± SD of 0.38 ± 0.09, during the period between start and end of chest closure. We will conservatively assume a standard deviation of 0.12 to begin the study, and re-evaluate the standard deviation during the first interim analysis. If a larger standard deviation is estimated, the sample size will be appropriately increased, with no statistical penalty. We further assume that we will have 2-3 cases per week, a within-cluster within-period correlation ρ of 0.10 and a within-cluster between-period correlation 0.01. With these assumptions and an average of 2.5 patients per week, total sample size needed will be 84 without adjusting for interim analysis, and 90 after adjusting for one interim analysis. Assuming 3 patients per week, the sample size needed will change to 88 before interim adjustment and 96 after adjusting for one interim[19]

Within-period and intra-period correlation will be also be assessed at interim analysis, and the total sample size will be adjusted if a larger within-period correlation or between-correlation were observed.

Future implications:

During this study, we will collect clinical outcomes, which will be presented in a descriptive analysis. They are listed under “exploratory endpoints” in the methods section. We plan to apply to the American Heart Association for a grant to support a future project which will examine clinical outcomes of cardiac surgery patients, who were treated with norepinephrine versus vasopressin.

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