# The Efficacy of Vasopressin in Critically Ill Patients with Pulmonary Hypertension: A randomized control study

*Renuka Jain*

## A. Study Purpose and Rationale

Pulmonary hypertension is a devastating disease with a fairly high mortality rate; these patients are particularly prone to complications from operative procedures, suffering a higher morbidity and mortality than patients without the disease. The challenge of managing these patients, post-operatively in the ICU setting, is balancing perfusion to vital organs with changes in pulmonary arterial pressures that may be hemodynamically significant. Standard of care has been the use of norepinephrine IV or vasopressin IV, although neither has been studied closely. Vasopressin has been offered as an ideal vasopressor for this population, hypothesized to increase peripheral resistance without increasing pulmonary arterial pressures, thus maximizing hemodynamics.

## B. Study Design and Procedure

This is a randomized control trial offered in two phases, all to be done at CPMC CT/SICU. All pulmonary hypertension specialists in this medical center will be made aware of study by letter, and information on contacting investigators should they have a patient that qualifies. Any patient meeting eligibility criteria, with pulmonary hypertension undergoing elective operation, will be recruited and approached in the Anesthesiology Suite and informed of the study. If they agree, informed consent will be obtained at that time by one of the physicians in the study or the study coordinator.

After informed consent is obtained, patients will undergo swan-ganz catheter placement prior to surgery. Intravenous access will be established in all patients prior to operation. These methods do not differ from standard pre-op care for patients with pulmonary artery hypertension.

### a. Phase I

A cross-over study, not randomized. Measurements of CVP, mean right ventricular pressure, mean pulmonary artery pressure, CO, CI, mean pulmonary wedge pressure will be obtained using standard techniques. During periods of hypotension, vasopressin will be administered. Measurements of pulmonary artery pressure, CO, CI, and wedge pressure will be obtained 1 minute after infusion.

### b. Phase II

Randomized study. Standard measurements from the swan-ganz catheter, as above, will be obtained. They will then be randomized to vasopressin or norepinephrine. Both subjects, anesthesiologist, and the ICU staff will be blinded. Only the study coordinator and primary investigator will have access to this information. Measurements will be obtained 1 min after infusion and then on standard 6 hour basis as per ICU protocol – all other vitals will be recorded as per ICU protocol. Nurses will be made aware of maximal titratable dose of each medication and a plan of safety will be formed in case of persistent hypotension, ischemia, end-organ damage. Parameters for discontinuing medication will be given to ICU staff.

## C. Study Drugs

Both vasopressin and norepinephrine are intravenous medications. They will be prepared in standard human dosages and medication level will be titrated to SBP > 95. Both medications can be prepared in the research pharmacy and blinded. Serious reactions to norepineprhine include hypertension, arrhythmias, asthma exacerbation, anaphylaxis. Serious reaction to vasopressin include myocardial infarction, bradycardia, hyponatremia, angina, arrhythmias, hypertension, bronchospasm, anaphylaxis,

angioedema, venous thrombosis. All are rare reactions, and a plan of safety will be constructued. Subjects may be unblinded and withdrawn from the study should these effects occur.

**D. Outcomes and Statistical Analysis**

The primary outcome of this study will be changes in pulmonary arterial pressure, as they have been shown to correlate with severity and prognosis of the disease.

Secondary outcomes will be changes in mean RV pressures, CO/CI, survival out of ICU, length of ICU stay. This study is not powered to examine mortality from pulmonary hypertension overall.

Results will be gathered by supervising physician and study coordinator. Results will be analyzed using paired t-test for phase I (cross-over, each subject is their own control), and unpaired t-test for phase II (two parallel arms used). In information gathered from prior cases of pulmonary hypertension in this institution as well as from animal data, assuming:

Norepinephrine change in PAP = 5 SD = 5

Vasopressin change in PAP = -2 SD = 5

Then, number of subjects required in phase I [(5/2)(5/2) 8 + 2 = 52 ] is 52 and in Phase II [(5/7)(5/7)16 +1 = 9] is 9 in each arm. Given that roughly 1-2 patients a month will qualify for this study, the projected time to completion (assuming 50% will go on to consent) is roughly 6 years. Numbers for phase II will be adjusted based upon results from Phase I.

**E. Subject Selection and Recruitment**

Inclusion: diagnosis of pulmonary hypertension by standard WHO RHC criteria. Undergoing elective operative procedure.

Exclusion: patients undergoing vascular surgeries (including valve repair, CABG, heart transplant), same day surgeries, those who will not be placed on epoprostenol IV prior to operation, ischemic heart disease, diagnosis of pulmonary hypertension secondary to left heart failure. Anyone with asthma or COPD will be excluded due to the potential exacerbation of asthma with norepinephrine.

**F. Recruitment:**

Discussed above

**G. Confidentiality of Study Data**

Subjects' personal identifiers will be removed from all copies of medical records obtained by investigator and unique codes will be assigned at enrollment. Only investigator and study coordinator will have access to all subject information

**H. Potential Conflict of Interest**

None

**I. Location of Study**

CPMC CT/SICU

**J. Potential Risks and Benefits**

Both vasopressor agents have side effects that will be closely monitored by standard ICU protocol. Long-term benefits include better understanding of pulmonary hypertension and its treatment.

**K. Compensation:**

No compensation nor cost to subjects is anticipated.