

Perioperative risk of heart failure patients undergoing major noncardiac surgery

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A. Study Purpose and Rationale

Over 10 million major non-cardiac surgical procedures were performed in the U.S. in 2000ⁱ There have been significant advances in the care of the perioperative patient undergoing non-cardiac surgery in the last two decades. These have primarily been aimed at the assessment and risk modification of those patients with coronary artery disease. Patients with heart failure (HF), however, represent an increasingly large and high risk population undergoing major non-cardiac surgery. HF is a major medical problem in the United States. There are over five million patients with HF in this country, and there are an estimated 555,000 new cases each year.ⁱⁱ The reason for the increasing incidence and prevalence of HF is likely multifactorial including improved therapies and survival of patients with chronic medical conditions such as atherosclerosis, hypertension, acute coronary syndromes and heart failure itself. Additionally, HF has a high prevalence among older individuals with 80% of cases occurring in patients 65 or older.ⁱⁱⁱ Older individuals are undergoing major non-cardiac surgery at increasing rates with 4 million major non-cardiac procedures performed each year.ⁱ

Patients with HF are at significant risk for life threatening perioperative complications. There are several widely used risk indices as well as practice guidelines that recognize HF as an important risk factor for adverse outcomes in the perioperative period. Currently, the ACC/AHA guideline for the cardiovascular assessment of the patient undergoing non-cardiac surgery^{iv} lists decompensated heart failure as a major clinical predictor and compensated or prior heart failure as an intermediate clinical predictor of poor outcome. Prior studies and recommendations have also recognized the importance of heart failure as a predictor of poor outcome in non-cardiac surgery. In 1977 Goldman, et al. published the original cardiac risk index for patients undergoing major non-cardiac surgery.^v Included in this index were clinical signs of heart failure including the presence of JVD or S3 gallop. In the Revised Cardiac Risk index HF remains as one of six important preoperative risk factors.

The data available for the assessment of risk and prevention of perioperative complications remain limited. In an ongoing retrospective review of patients with heart failure who underwent intermediate to high risk non-cardiac surgery at our institution (n=134), 27% of patients had at least one perioperative event including death (7.5%), non ST-segment elevation MI (14.2%), ST elevation MI (1.2%), and HF exacerbations (21%).

Advances in therapeutic and diagnostic modalities in the treatment of HF including medical therapy such as vasodilator therapy, beta adrenergic antagonism and neurohormonal blockade, as well as serum studies such as BNP may prove useful in the evaluation and prevention of cardiac risk in patients undergoing non-cardiac surgery. HF remains a clinical diagnosis, however B-type natriuretic peptide (BNP) levels have been shown to be useful in determining HF as a cause of dyspnea in patients presenting to the emergency room.^{vi} Furthermore, high levels of plasma BNP have been correlated with morbidity and mortality in patients with asymptomatic or minimally symptomatic HF,^{vii} and BNP levels vary largely within a population of patients with heart failure.^{viii} The levels have not been evaluated with regard to non-cardiac surgery. Other clinical signs of decompensated cardiac failure such as the S3 gallop (used in the initial cardiac risk index) have been shown to have poor inter-observer agreement.^{ix} Phonocardiography is considered the gold standard for detection of an S3 and is relatively simple to perform, but is generally not used in the assessment of patients with HF.

Patients with HF represent an important and high risk group undergoing major non-cardiac surgery. Specific risk factors and novel indexes have not yet been developed to predict adverse outcomes in this cohort of patients. Furthermore, recent advances in the treatment and evaluation of patients with

HF have not yet been evaluated in the perioperative setting. I propose a prospective study to evaluate the demographic and clinical characteristics of patients with HF undergoing non-cardiac surgery as well as to evaluate their post surgical course. This study will validate risk factors identified in an ongoing retrospective analysis, associated with peri-operative complications; medications that correlate with poor or improved outcome and additionally specifically evaluate two markers of decompensated heart failure (serum BNP levels, and phonocardiographic S3) as risk factors for poor outcomes in patients undergoing major non-cardiac surgery^x

B. Study Design and Statistical Analysis:

This is a prospective observational cohort study of patients undergoing intermediate or high risk non-cardiac surgery and meet the Framingham Criteria for Heart Failure (attached). Surgeries will include peripheral vascular surgery (including vascular bypass, as well as amputations excluding toe and foot amputations), major intrabdominal or intrathoracic surgery, radical prostatectomy, orthopedic surgery, carotid endarterectomy, head and neck surgery as were characterized by Eagle, K, et al.^{xi}

The primary endpoint will be a combination of death, myocardial infarction (defined by elevated troponin), and worsening of heart failure (defined by increasing or new rales on exam or new/worsening pulmonary vascular congestion, a decrease in blood pressure by 25% from baseline, worsening of renal function by 50% or need for inotropic therapy).

A multivariable logistic regression will be used to identify risk factors for the primary outcome in the ongoing retrospective study. In this study those variables/risk factors identified in the retrospective study will be validated using single variable and multivariable logistic regression.

Additionally, a chi squared test of the presence of phonocardiographic S3 and serum BNP levels above 230 pg/ml. These variables will also be included in the multivariable logistic regression.

The prevalence of an S3 gallop in patients with HF varies widely (20-68% depending on patient population, i.e. in patient's with EF30% or less prevalence was 68%)^{xii,xiii} published literature. In our retrospective study, the presence or absence of an S3 was not mentioned specifically in the vast majority of cases reviewed. It is reasonable to assume a prevalence of around 50% for all comers, especially if phonocardiography is used. In Goldman's original cardiac risk index, the presence of an S3 was associated with a life-threatening cardiac complication or death in 34% vs. 14% without. To detect a difference this large with an alpha of <0.05 and 80% a sample size of 160 subjects (80 in two equal groups) is needed. For a more modest but still clinically relevant difference a set alpha of 0.05 and 80% power, using the retrospective data to predict an approximate event rate, a difference of 10% could be detected with a sample size of approximately 360 subjects.

The median level for BNP in the serum of patients with chronic heart failure is 231pg/ml. If patients are grouped into two cohorts (above and below this level), 360 subjects will be needed to detect a 10% difference for set alpha of 0.05 and 80% power. The study will enroll 360 emergent surgeries in order to eliminate selection bias that may have been present in the retrospective study. However, all patients who qualify will be approached for entry into the study, and analysis will be performed on the group as a whole as well as those undergoing emergent surgery alone.

C. Study Procedure

After subjects are identified prior to surgery, approached, meet the requirements of the study, and give informed consent (see procedure below), they will undergo a focused medical history and exam on the day prior to or the day of the index surgery as well as on post operative day (POD) #1 which will include auscultation and recording of heart sounds with an electronic stethoscope (Welch Allyn Master Elite Electronic Stethoscope). This data will then be downloaded onto a computer and analyzed using Welch Allyn® Master Elite Analyzer Model 5079-402 which allows for phonocardiographic evaluation

along with synchronized ECG analysis obtained from a single channel, three lead ECG wire, embedded in the stethoscope, for the presence of an S3 gallop.

Two BD Vacutainer® spray-coated K₂EDTA lavender top tube of blood (2ml) will be obtained and b-type natriuretic peptide assay manufactured by Abbott Diagnostics (quality assurance and clinical performance data available online at:

http://www.abbottdiagnostics.com/About_Us/AACC/abstracts/F_BNP_%20Assay_Poster_7-7.pdf will be used to analyze BNP levels. The first sample will be obtained the day prior to or the day of the index surgery. A second sample will be obtained on POD #1

Demographic information and pre and post-op clinical information identified during the ongoing retrospective trial will be obtained either from a review of the patient's medical record, or if not obtained and recorded by the primary team during routine course of treatment, during the focused history and exam. Aside from BNP levels and phonocardiographic exam, no additional laboratory or diagnostic studies (i.e. blood or body fluid samples, radiographs, cardiac stress testing, EKGs, echocardiogram or cardiac catheterization) will be obtained except as is clinically indicated and ordered by the primary team. The information obtained may include any of the following currently being analyzed and includes:

1. Clinical/Demographic characteristics: Age, race, gender, NYHA Class of HF, symptoms of preoperative fatigue (present or not by clinical history), dyspnea (present or not by clinical history), and angina (present or not by clinical history), history of an MI (defined in history, Q waves on EKG, and/or wall motion abnormality on echo), prior coronary artery bypass surgery, prior valve surgery and history of HTN (defined by a SBP > 140/90 or the use of antihypertensive medications), Diabetes mellitus (defined by the use of oral agents or insulin, HbA1c > 6.0, or random sugar > 200 mg/dl) or peripheral vascular disease (defined by the history or evidence of an angiogram done preoperatively, claudication, previous amputation, or ABI < 1.0 by non-invasive flow studies), history of arrhythmias (VT/SVT) or the presence of an AICD.
2. Physical Exam: The following preoperative (one day prior to or on the day of surgery) and post operative physical exam findings will be recorded including vital signs (heart rate, blood pressure, respiratory rate, oxygen saturation) lung exam (rales or not), presence of S3 (by analog or electronic auscultation) or JVD, liver size and hepato-jugular reflex, and 1+ or > edema.
3. Laboratory Tests: Preoperative and postoperative laboratory tests including hemoglobin, hematocrit, PT/PTT, BUN and creatinine (creatinine clearance using the cockcroft-gault will be calculated), blood sugar, liver function tests and troponin will also be extracted from data obtained during routine care.
4. Non-invasive and Invasive Testing: The following results of preoperative and postoperative tests will be recorded:
 - a. Echocardiography: (LVEF and LVEDD, regional wall motion abnormalities, valvular pathology {(all four valves and degree of either regurgitation or stenosis), hypertrophy, RVSP, RV function},
 - b. Stress test: type (exercise/pharmacologic), supplemental imaging (echo, nuclear), exercise duration (minutes and METS), resting HR, resting BP, peak exercise HR, peak exercise BP, double product, reason for stopping (SOB, angina, claudication), ischemia (Y/N), single or multiple territories, ECG evidence of ischemia
 - c. Catherization: (LVEF and extent of CAD),
 - d. Chest x-ray: pulmonary vascular congestion, cardiomegaly
 - e. EKG: (rate, rhythm, & QRS duration, Q waves, old infarcts, LBBB/RBBB)
 - f. Use of preoperative Swan-Ganz catheter and relevant variables including PCW, PA pressure, cardiac output).
5. Medications: The dose, route, frequency and duration of medications taken by the subject beginning the day prior to surgery until the time of discharge.

Additional information on the intraoperative and post operative course recorded or obtained during the focused history and physical will include:

6. Intra-operative:
 - a. The type of anesthesia used for the surgery and the use of intraoperative nitrates and beta-blockers.
7. Post operative events:
 - a. Clinical characteristics including symptoms of fatigue (present or not by clinical history), dyspnea (present or not by clinical history), angina (present or not by clinical history), morbid events (see below) occurrence of arrhythmias (VT/SVT/VF). The need for an ICU stay (and number of days), the need for blood transfusion (and number of units) and the total length of stay.

At the time of discharge or upon the death of a study subject the patient's medical record will be reviewed for the presence of the combined endpoint as specified above. If necessary, the patient will be approached to confirm the presence or absence of the primary endpoint.

For certain clinical variables, it is possible that differences in exam style and proficiency among the study investigators may introduce systematic bias. The measurement of JVP is particularly subject to this variability. In order to assess for inter-observer variability in physical exam findings, ten additional subjects admitted to the hospital with a diagnosis of heart failure will be assessed by all three of the study investigators performing the exams. Assessment of JVP will be performed by elevation of the head of the bed to 45 degrees, with subsequent assessment of the internal jugular vein filling height above the sternal angle in centimeters. To this height five centimeters will be added to account for the distance of the sternal angle above the right atrium. If satisfactory inter-observer concordance is not achieved, an additional ten subjects will undergo the same evaluation until the exams are concordant.

D. Study Drugs

N/A

E. Medical Devices

Welch Allyn Master Elite Electronic Stethoscope and Welch Allyn® Master Elite Analyzer Model 5079-402 will be used for auscultation of subjects' heart sounds as well as phonocardiographic analysis to assess for presence of an S3 gallop.

F. Study Questionnaires

N/A

G. Study Subjects

Subjects will qualify for the study if they are admitted to undergo one of the procedures specified above either as emergent, urgent or elective surgery; and have heart failure. The diagnosis of heart failure will be made based on the modified Framingham Criteria (attached). Exclusions will include those subjects with a history of organ transplantation or with end stage renal disease on dialysis (CKD 5).

The study is not restricted by gender, race, ethnicity, language spoken, or age.

H. Recruitment of Subjects

Subjects for will be identified and approached by one of three methods.

1. Senior medical residents on the medical consultation service called to consult for pre-operative evaluation will identify patients with a prior or suspected diagnosis of heart failure. The resident will then page a prespecified pager that will be held at all times by one of three members of the

investigative team. The investigators will then contact the primary team responsible for the care of the patient. The primary team will approach the patient regarding the study. If the patient agrees, the patient will be approached by the investigators. The subject will then be screened for study admission (i.e. type of surgery, Modified Framingham criteria, and exclusion criteria). If the subject qualifies for the study, informed consent will be obtained and the study protocol carried out.

2. An automated system would be in place that would activate the investigator's pager when a patient with a prior clinic visit or hospital admission under the ICD-9 for HF (428.X) in the prior two years was admitted to a surgical floor. A preliminary review of the patient's chart will then be performed for initial assessment of subject qualification (i.e. admission for one of the index operations, exclusion criteria). If the subject passes the initial screen, the investigators will then contact the primary team responsible for the care of the patient. The primary team will approach the patient regarding the study. If the patient agrees, the patient will be approached by the investigators. The subject will then be screened for study admission (i.e. type of surgery, Modified Framingham criteria, and exclusion criteria). If the subject qualifies for the study, informed consent will be obtained and the study protocol carried out.
3. A review of the surgical cases for the specific week and the surgical schedule for each week will be continuously reviewed as the list is updated. Patients will be eligible if they have had a physician visit or hospitalization for HF (ICD-9 428.X) in the two-year period prior to the operation and are scheduled for one of the index operations. A preliminary review of the patient's chart will then be performed for initial assessment of subject qualification (i.e. admission for one of the index operations, exclusion criteria). If the subject passes the initial screen, the investigators will then contact the primary team responsible for the care of the patient. The primary team will approach the patient regarding the study. If the patient agrees, the patient will be approached by the investigators. The subject will then be screened for study admission (i.e. Modified Framingham criteria, and exclusion criteria). If the subject qualifies for the study, informed consent will be obtained and the study protocol carried out.

I. Confidentiality of Study

Each patient will receive a unique coded identifier. Data will be stored in a secure location and be password protected with access granted only to investigators.

J. Location of the Study

The study will be performed in the clinical areas of CPMC including Milstein Hospital and the Allen Pavilion.

K. Potential Risks

The study has limited risks to the patient. There is a small risk associated with the additional blood draw for assessment of serum BNP concentration. There is no risk associated with the focused history and physical exam performed by the investigators.

L. Potential Benefits

Though there would be limited communication between the investigators and the primary surgical team, there is a potential benefit to the increased medical attention received by the subjects of the study.

M. Alternative Therapies

N/A

N. Compensation to Subjects

The subjects will not be compensated for their participation.

O. Costs to Subjects

There will be no cost to the study participants.

P. Minors as Research Subjects

N/A

Q. Radiation or Radioactive Substances

The study will not expose the subjects to any additional radiation that is not part of the subjects' clinical management.

R. References

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Framingham Criteria for Congestive Heart Failure

Major Criteria

Paroxysmal nocturnal dyspnea

Neck vein distension

Rales

Radiographic Cardiomegaly

Acute pulmonary edema

S3 gallop

CVP>16 cm H2O

HJ reflux

Pulmonary edema/vascular congestion or cardiomegaly at autopsy

Weight loss >4.5kg in 5 days with response to diuretic

Minor criteria

Bilateral ankle edema

Nocturnal cough

Dyspnea on exertion

Hepatomegaly

Pleural effusion

Tachycardia