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Changes to Echocardiography-Derived Left Ventricular Filling Pressures and Cardiac Output in Response to Fluid Boluses in Elderly Patients with Left Ventricular Diastolic Dysfunction Undergoing Vascular Surgery

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**CHANGES TO ECHOCARDIOGRAPHY-DERIVED LEFT VENTRICULAR
FILLING PRESSURES AND CARDIAC OUTPUT IN RESPONSE TO
FLUID BOLUSES IN ELDERLY PATIENTS WITH LEFT VENTRICULAR
DIASTOLIC DYSFUNCTION UNDERGOING VASCULAR SURGERY**

by

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A THESIS

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for the Degree of Master of Science

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CHANGES TO ECHOCARDIOGRAPHY-DERIVED LEFT VENTRICULAR FILLING PRESSURES AND CARDIAC OUTPUT IN RESPONSE TO FLUID BOLUSES IN ELDERLY PATIENTS WITH LEFT VENTRICULAR DIASTOLIC DYSFUNCTION UNDERGOING VASCULAR SURGERY

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University of Nebraska, 2016

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Left ventricular diastolic dysfunction (LVDD) of the heart is a condition where the heart does not relax properly. This condition is important during times of stress, as LVDD is associated with significant morbidity of elderly surgical patients. LVDD is often asymptomatic and unrecognized as many of these patients have normal ejection fractions. However, LVDD may lead to heart failure in patients with preserved systolic function, with the incidence being as high as 50% in hospitalized elderly patients. The diagnosis of LVDD is an independent risk factor for postoperative major adverse cardiac events (MACE) and negatively impacts post-surgery readmission rates.

Anesthesiologists play a critical role in the care of elderly patients by managing fluid therapy during surgery. Current standard of care is to manage elderly patients with LVDD using only blood pressure monitoring. Unfortunately blood pressure monitoring is unable to detect changes in diastolic function, which fluid administration may affect. In contrast, transesophageal echocardiography (TEE) can easily measure diastolic function in real-time in the operating rooms. No current studies, however, have assessed changes to diastolic function in response to fluid boluses during noncardiac surgery. Therefore, it is important to serially evaluate LVDD intraoperatively with TEE and determine if changes in anesthetic management, specifically the response to fluid boluses, has effects on diastolic indices. The specific aim of this study is evaluate

changes in left ventricular filling pressures and cardiac output in response to fluid boluses during the perioperative period. We predict echocardiographic diastolic indices are influenced by intraoperative fluid administration.

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LIST OF ABBREVIATIONS

LVDD	left ventricular diastolic dysfunction
HF	heart failure
MACE	major adverse cardiac events
CO	cardiac output
ECG	electrocardiogram
PACs	pulmonary artery catheters
TTE	transthoracic echocardiography
ASE	American Society of Echocardiography
TEE	transesophageal echocardiography
OR	operating room
SV	stroke volume
SHEM	<u>S</u> tandard <u>H</u> emodynamic <u>M</u> anagement
EGHEM	<u>E</u> cho- <u>G</u> uided <u>H</u> emodynamic <u>M</u> anagement
CHF	congestive heart failure
A Fib	atrial fibrillation
mL	milliliters
kg	kilogram
HFpEF	heart failure with preserved ejection fraction
GDT	goal directed therapy
NPO	nothing by mouth
E/e'	left ventricular end diastolic pressure
PASC	Preanesthesia Screening Clinic
AAA	abdominal aortic aneurysm
EVAR	endovascular aortic repair
LEB	lower extremity bypass
e'	lateral mitral annular tissue Doppler velocity
E	peak early mitral inflow velocity
A	peak late mitral inflow velocity

AV	aortic valve
C	chamber
LAX	long axis view
ME	midesophageal
SAX	short axis view
VTI	velocity time integral
LVOT	left ventricular outflow tract
E velocity	peak mitral early inflow velocity
ME 4C	Midesophageal 4 Chamber
T ₀	Time zero
NS	normal saline
BMI	body mass index
CAD	coronary artery disease
COPD	chronic obstructive pulmonary disease
LE	lower extremity
SD	standard deviation
L/min	liters/minute
LVEDP	Doppler-derived LV filling pressure

CHAPTER 1: INTRODUCTION

Left ventricular diastolic dysfunction (LVDD) is a common disease in the rapidly growing elderly patient population and a major risk factor for heart failure (HF)^{1,2 3,4,5} In the United States, more Medicare dollars are spent on the diagnosis and treatment of HF than any other diagnosis.⁶ A recent study of 1000 elderly surgical patients found that LVDD was found preoperatively in 50% of patients undergoing vascular surgery, of which 80% were asymptomatic.^{7,8} Often asymptomatic, LVDD is an independent predictor of postoperative morbidity and mortality.^{9,10,11} Echocardiography is noninvasive and can measure diastolic function in real-time during the perioperative period. However, randomized clinical trials describing the use of echocardiography to guide intraoperative management have not been reported.⁸ Based on pilot data, we believe echocardiography-derived diastolic indices are influenced by anesthetic management; thus monitoring these indices and adjusting clinical algorithms accordingly can affect risk of postoperative major adverse cardiac events (MACE).

LVDD and Anesthetic Management

The goal of anesthesiologists taking care of elderly surgical patients is to maximize the patient's circulatory function by optimizing cardiac output (CO) and ventricular filling pressures. The use of electrocardiogram (ECG) monitoring and systemic blood pressure is the standard of care for assessing circulatory function. However, these measurements are not barometers of diastolic function. Even the most invasive monitors, such as central venous pressure and pulmonary artery catheters (PACs), lack the ability to evaluate diastolic function and have not been shown to improve survival in elderly surgical patients.^{9,12} Because of the invasive nature of PACs and a lack of supportive evidence, they are not used in most noncardiac surgeries. Management of

these high-risk patients is left to noninvasive blood pressure monitoring, which can only serve as a surrogate measurement of filling pressures and CO.

LVDD and Fluid Management

Anesthesiologists are the perioperative primary care physicians of elderly patients undergoing more than 14 million procedures a year. They guide fluid management, alter vascular compliance, and treat sympathetic stimulation—all of which may impact clinical outcomes in patients with LVDD.¹³ With a diagnosis of diastolic dysfunction, a person accumulates approximately \$110,000 in medical expenses over an average of four years from diagnosis to death. The average estimated LVDD-related hospitalization charge is \$73,762 per person, with outpatient costs exceeding \$25,000 per person.⁶ While it is known that these older patients often have LVDD and that LVDD is an independent risk factor of mortality, it is not known how LVDD changes under standard operating conditions or if those changes influence or predict clinical outcomes.^{14,15} Standard guidelines or consensus statements on how to manage perioperative LVDD do not exist, despite billions in yearly health care expenditures.⁴ Current anesthesia standards of care for fluid and drug management is no different in the elderly patient than the younger patient, even though elderly patients with LVDD undergoing surgery may need different fluid and drug management to optimize loading conditions.

Background

Previous investigations have shown that varying degrees of LVDD carry different risks of mortality; therefore, the ability to detect patients who are considered “high-risk” may lead to a change in current anesthesia practice. In a cross-sectional population study done by Redfield and colleagues in over 2,000 people aged 45 years or older, the

prevalence of diastolic dysfunction was over 20 percent and had an 8.31 times higher risk of mortality. Those with moderate (6.6% prevalence) and severe LVDD (0.7% prevalence) had 10.2 times higher mortality at 5 years compared with those with normal diastolic function.⁴ Grading of LVDD is commonly based on echocardiographic schema using transthoracic echocardiography (TTE). Guidelines from the American Society of Echocardiography (ASE) classify diastolic dysfunction into Grades I (Impaired Relaxation), Grade II (Pseudonormal) or Grade III (Restrictive).¹⁶ This grading system is often used to assess response to therapy in epidemiological studies with TTE; however, the utility for assessment of LVDD with transesophageal echocardiography (TEE) has recently been studied during cardiac surgery by Swaminathan and colleagues.^{5,15} Their retrospective study of over 900 patients found that a simple echo algorithm increased classification of LVDD and that worsening grades of LVDD were associated with higher adverse events.¹⁵

Significance

Although the grading of LVDD may differ in the operating room (OR) versus a “snapshot” on a screening TTE, studies into whether diastolic function can actually worsen or improve during surgery in response to fluid and drug therapy have not been completed. Although it is known that a worsening LVDD grade has a negative impact on mortality, it is not known how often the grade of LVDD changes in the dynamic operative room environment. Secondly, if LVDD grades are dynamic during surgery, can alterations in fluid and drug therapy based on these changes affect outcomes? This study will address these key questions:

How does LVDD change in response to standard anesthesia management and surgical stimuli?

Our ability to detect and managing LVDD in the dynamic state of the OR is lacking.¹⁷ Few studies have been published on the effects of anesthetic drugs on LVDD since the early 1990s, when Pagel published his work describing the effects of inhaled anesthetics on LVDD in animal models using invasive catheter measurements.^{18,19,20} Anesthesiologists are the gate-keepers of two important variables that affect loading conditions in the OR: fluids and drugs. Ongoing adjustments in fluid and drug therapy may have significant effects on underlying LVDD.

Current anesthesia practice is to treat elderly patients with the same fluid management strategies as younger ones. Fluids are not set on a pump, but rather “free-flowing” at the discretion of the provider. Are there optimal fluid and drug therapies that should be targeted for elderly patients with LVDD undergoing noncardiac surgeries, as it is known these patients are “high-risk,” even though it is “low-risk” surgery?²¹ Could noninvasive Doppler, as opposed to invasive catheter measurements, improve care?

Can echocardiography be used to guide fluid and drug management during surgery LVDD patients?

In the perioperative setting, using echocardiography to understand how elderly at-risk patients, with known preoperative evidence of LVDD, react to standard anesthesia management and surgical stimuli would be highly valuable and contribute to the limited body of knowledge on intraoperative diastolic dysfunction and management. Recent studies in goal-directed fluid management suggest that patients who receive fluids based on targeted left ventricular stroke volume (SV) measurements have improved outcomes compared to patients receiving liberal or “recipe” fluid management strategies. Several studies suggest that optimization of fluid management can reduce perioperative cardiovascular morbidity and shorten

hospital stay.^{22,23,24} Intraoperative TEE can calculate left ventricular SV based on adjustments in fluids or drug therapy and may help define target therapy for patients with LVDD.

Preliminary Studies

The primary and secondary investigators completed a prospective, randomized, IRB-approved pilot study of 28 surgical subjects identified in pre-anesthesia clinic using TTE to have LVDD.²⁵ Subjects were screened on the basis of age > 65 years or younger subjects with age-related cardiovascular phenotype. Average subject age was 69.7 years (10 male, 18 female) and average body mass index (BMI) was 30.9 kg/m².²⁵ Thirteen noncardiac surgeries were used for inclusion criteria, based on a previous study done by Hammil.³ Subjects were identified to have LVDD using assessment criteria based on guidelines from the ASE on the grading of LVDD.¹⁶ Subjects were randomized into two groups: a Standard Hemodynamic Management group (SHEM) versus an Echo-Guided Hemodynamic Management (EGHEM) group. Subjects in the EGHEM group (n=14) received intraoperative TEE to manage fluids and optimize CO using left ventricular filling patterns.

Preliminary Study Changes in LVDD

It was noted in the EGHEM group that seven of 14 subjects (50%) had no change in LVDD grade intraoperatively while six (43%) had improvement in LVDD grade, and one subject (7%) worsened in LVDD grade. This led us to question the properties of diastolic indices, normally used to screen patients as a one-time measurement in awake, spontaneously breathing patients. Our preliminary data suggests that patients undergoing surgery may change their grade of LVDD and

supports the hypothesis that diastolic dysfunction is dynamic in the OR. This finding lent itself to investigate the dynamic nature of LVDD perioperatively.

Preliminary Study Changes in Fluid Management

One of the secondary aims of the preliminary study was to measure the difference in the frequency of congestive heart failure (CHF) and atrial fibrillation (A Fib) postoperatively between the two groups: subjects who underwent SHEM versus subjects who underwent EGHEM. The incidence of CHF at 30 days was 21.4% in the SHEM group and 7% in the EGHEM group.

The incidence of A Fib at 30 days was 28.6% in the SHEM group and 14.3% in EGHEM group (Figure 1).²⁵

One statistically significant difference between the control and intervention group was the amount of intraoperative fluid administered based on the clinical algorithm. The EGHEM group received 12.7

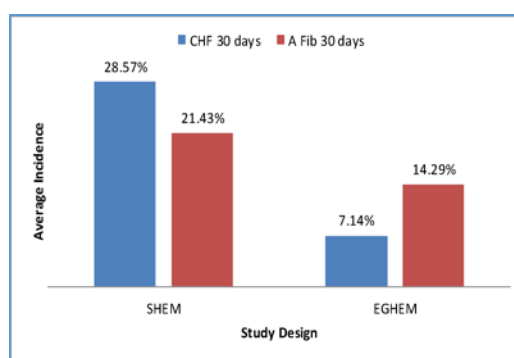


Figure 1: Pilot Study. This graph demonstrates the finding of the pilot study where clinical outcomes at 30 days post op of CHF and A Fib showed a trend towards decrease in the interventional group (EGHEM) who received less fluids when compared to the control group (SHEM).

milliliters(mL)/kilogram(kg) of intraoperative intravenous fluid, while the SHEM group received 33.04 mL/kg ($p=0.017$).²⁵ This led to the following question: what is the exact response of fluid to diastolic echocardiography indices and left ventricular CO? Does fluid administration improve or worsen either measurement? This question led us to specifically determine if goal-directed echocardiography-guided hemodynamic management of LVDD in elderly surgical patients can change intraoperative diastolic function.

Perioperative Fluid Management and LVDD

It is understood that LVDD can lead to heart failure with preserved ejection fraction, often called HFpEF. While the clinical treatment of LVDD is unclear, the treatment of CHF, either systolic or diastolic, is aimed at decreasing afterload and preload with the goal of lowering left-sided filling pressures and promoting forward flow to improve organ perfusion. Optimizing fluid to minimize pulmonary congestion and peripheral edema is an important part of the treatment and avoidance of clinical heart failure. Utilization of diuretics is often the mainstay of therapy to prevent and or treat CHF. Specific clinical trials looking at the treatment of diastolic heart failure have included diuretics, beta-blockers, angiotensin converting enzyme inhibitors, drugs to control heart rate and prevent myocardial ischemia, and drugs to promote cardiac hypertrophy and remodeling such as phosphodiesterase-5 inhibitors and statins. The prevention of perioperative diastolic heart failure, however, has not been addressed in previous clinical trials. The question of what amount of intraoperative fluids should be given to patients that have LVDD undergoing surgery has not been addressed.

In the last 10 years there has been a significant amount of literature looking at “restrictive” fluid therapy versus “liberal” fluid therapy versus “goal directed therapy” (GDT) in patients undergoing cardiac and noncardiac surgery. The majority of the literature in noncardiac surgical patients has been performed in major abdominal surgery. These studies performed in abdominal surgical cohorts have shown improved outcomes when GDT is used.^{22,23,24} Little is known on the effects of GDT in patients undergoing vascular with known diastolic function or impaired relaxation of the left ventricle.

In 2015 the International Fluid Optimization Group published a consensus statement on perioperative fluid therapy recommendations.²⁶ While the document points out that over or under hydration of perioperative patients is harmful, the most important analysis point to the fact that as clinicians, our ability to recognize and measure fluid sensitivity is often wrong. Previously perpetuated dogma of fluid therapy based on “nothing by mouth” (NPO) status, preoperative state, and the patient’s weight are unfounded and have little to no scientific evidence.²⁶ At the same time, there is vast variability of fluid treatment and algorithms amongst institutions and practitioners, making research studies difficult.^{27,28,29} And what we have always learned as to exist as the “third space” has been abandoned.

Arterial compliance (change in volume over a change in pressure) decreases as stiffness of the vasculature increases with aging. In patients with peripheral vascular disease, this is an added detriment to the patient’s ability to adapt to changes in vascular tone due to anesthetics. There are dynamic noninvasive measurements of “fluid responsiveness” that can be used in cases of hemodynamic instability to assess patient’s fluid status in the OR. These include pulse pressure variation, systolic pressure variation, and SV variation. If greater than 20% in patients on positive pressure ventilation, these may point to patients who are “fluid responders”. It is important to note that these 25% of patients under general anesthesia are in what is known as the “gray zone”, between 8-15%.³⁰ As such, these indirect measurement of fluid responsiveness may not be accurate or possible in a quarter of patients in the OR.

A fluid bolus challenge, particularly using the passive leg raise test, may be the safest way to measure fluid responsiveness in patients that are undergoing surgery and are hemodynamically unstable and the question whether a fluid bolus is indicated. Mini-

boluses, such as 50-100cc, are also more recently being studied, as more and more literature points to over hydration with previously larger boluses (500mL or more) may be detrimental to patients who are undergoing surgery that are hemodynamically unstable.

It is important to recognize that because a patient may be a fluid responder, it does not mean that fluid is necessary or needed. Low vascular tone, or low cardiac contractility may need to be addressed in order to improve ventricular filling.

The recent consensus statement on perioperative fluid therapy recommended three things be present to safely administer fluids: the need for hemodynamic improvement, the presence of fluid responsiveness, and the lack of associated risk. Since fluid therapy in the elderly population with LVDD has not been studied, we do not know the associated risk of giving fluid to these patients. We know that elevated LV pressures are associated with poor outcomes, and that diastolic dysfunction is a precursor to diastolic heart failure, and that diastolic heart failure is treated with decreasing afterload and improving arterial compliance and decreasing LV filling pressures to improve coronary perfusion. We know the presence of LVDD increases perioperative mortality, and the treatment of HFpEF involves limiting fluid therapy and providing diuresis.^{1,2,3,4,5,31,32,33,34} The proposed research allowed us to begin to understand this risk by evaluating the relationship between LV filling pressures, left ventricular CO, and perioperative fluid management.

Primary Study Objective and Hypothesis

The primary **objective** of the study was to describe how moderate size fluid boluses changed CO in elderly vascular surgery patients with LVDD. Our secondary objective was to evaluate how moderate size fluid boluses change E/e' in elderly patients undergoing vascular surgery that have baseline elevated LV filling pressures (Grade II or Grade

III LVDD) or normal filling pressures with evidence of Grade I LVDD. We performed a prospective clinical trial to evaluate the effect of fluid boluses on intraoperative echocardiography diastolic measurements of LVDD including CO and E/e' in elderly vascular surgical patients who have baseline LVDD. The clinical trial was a substudy of a larger NIH funded grant studying the effects of an echo-guided treatment algorithm on patients undergoing vascular surgery who had known LVDD (1R03 AG045103-01A1), Principle Investigator: Sasha K. Shillcutt, M.D. We used an echocardiography-driven algorithm to administer fluid boluses and measured both E/e' and left ventricular CO intraoperatively on TEE during vascular surgery.

Specific Aim 1

To describe how moderate size fluid boluses change CO in patients with baseline elevated LV filling pressures (Grade II or Grade III LVDD).

Specific Aim 2

To describe how moderate size fluid boluses change E/e' in elderly patients undergoing vascular surgery that have baseline elevated LV filling pressures (Grade II or Grade III LVDD) or normal filling pressures with evidence of Grade I LVDD.

We assessed changes in LVDD in the subjects by administering a series of 250 mL fluid boluses prior to surgical incision on elderly patients undergoing vascular surgery. We then measured changes in both filling pressures and CO in the subjects.

CHAPTER 2: METHODS

Study Design

The study was a controlled, single-blind prospective clinical trial in patients age 60 years or older with echocardiographic evidence of Grade I, II or III LVDD on preoperative TTE. All study protocols were approved by the Institutional Review Board at the University of Nebraska Medical Center.

Study Population

Study population included patients undergoing vascular surgery 60 years of age or older at the University of Nebraska Medical Center. Screening took place in the Preanesthesia Screening Clinic (PASC) outpatient clinic. The study population included both male and female patients age 60 years or older who had echocardiographic evidence of Grade I, II or III LVDD on preoperative TTE examination and met inclusion/exclusion criteria (Table 1). The subjects were undergoing any one of the vascular procedures listed below.

1. Open abdominal aortic aneurysm (AAA) repair
2. Endovascular aortic repair (EVAR)
3. Lower extremity bypass (LEB)

Inclusion and Exclusion Criteria

The inclusion criteria and exclusion criteria of the study subjects are listed in Table 1 below.

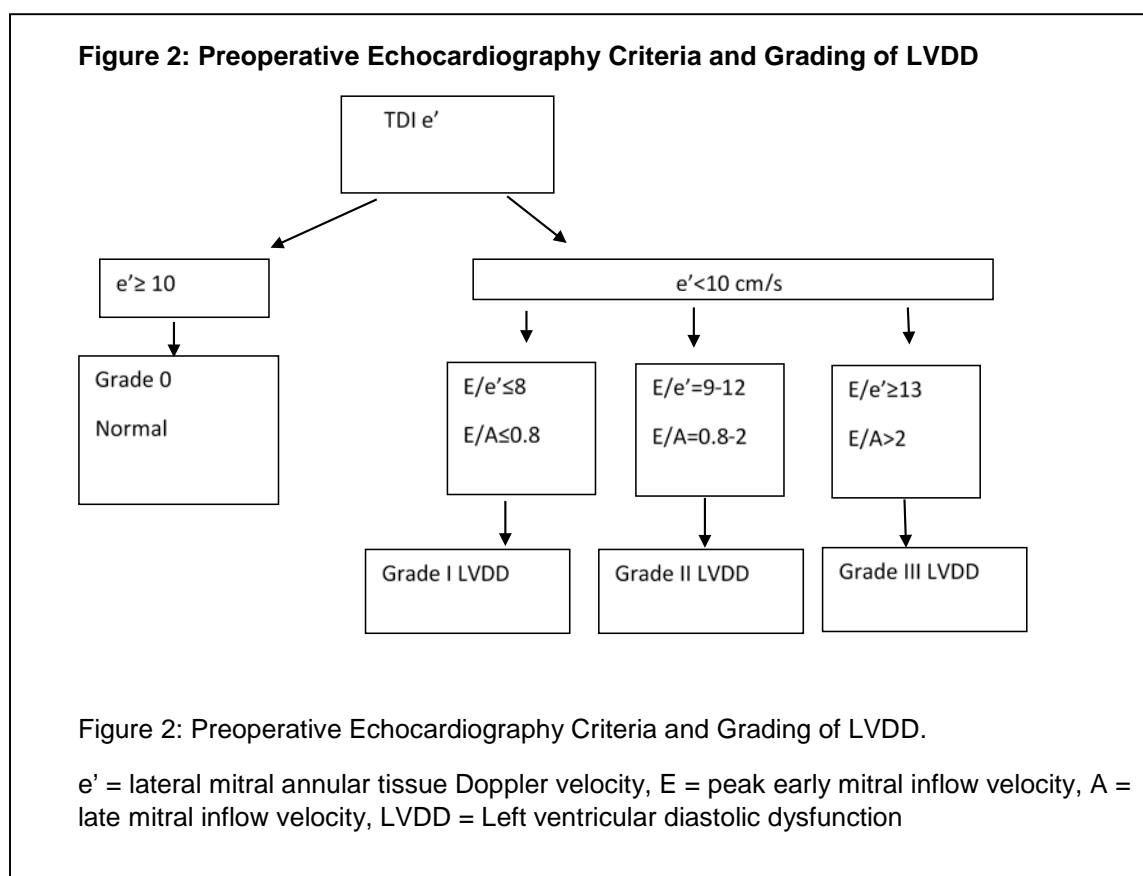
Inclusion Criteria	Exclusion Criteria	Exclusion Justification
Age 60 years and older	Patients with expected hospital stay < 24 hours	Inability to assess outcome measures
Echocardiographic Evidence of Grade I, II or III LVDD on Preoperative TTE examination	Inability to undergo TEE and TTE	Inability to obtain echo measurements
	Clinical evidence/suspicion of elevated ICP	Increase risk of decreased brain perfusion
Undergoing vascular procedures listed below: 1. Lower extremity bypass (LEB) 2. Open abdominal aortic aneurysm (AAA) repair 3. Endovascular aortic repair (EVAR) 4. Ability to read, understand, and sign consent form	Preoperative shock or systemic sepsis	Inability to properly consent patients
	Emergency operation	Inability to properly consent patients
	American Society of Anesthesiologists Status V	Inability to properly consent patients
	Participation in another clinical trial	Interference with study findings

Table 1: Study Inclusion and Exclusion Criteria

Study Enrollment

Potential study subjects were approached during their pre-surgical visit in the PASC by study investigators based on inclusion/exclusion criteria. Once informed consents were obtained, eligible patients underwent a screening TTE. Further enrollment into the study then required TTE evidence of LVDD based on echocardiography criteria

for LVDD (see Figure 2). Subjects were then given a screening grade of LVDD (I, II or III) as described in Figure 2. The primary Grade of LVDD was given based on e' , then E/e' . While E/A ratio was considered as a secondary factor, LVDD Grade was assigned based on E/e' only.



Echocardiography Data Points

The first TTE completed was considered the screening TTE in the PASC, and labeled as such. Immediately prior to induction of anesthesia and the day of planned surgery, another TTE was performed to collect diastolic indices listed in Table 2 and labeled as the baseline TTE. This baseline TTE was done the day of surgery to ensure that any differences in diastolic indices noted on intraoperative TEE when compared

to the screening TTE were less likely to be influenced by NPO status.

Table 2: Echocardiography Data Points Collected during Screening TTE, Baseline TEE and Intraoperative TEE Examination

Echocardiography	Screening TTE	Intraoperative TEE
Left Ventricular Wall	Parasternal SAX	Assessed by TTE only
Left Atrial Volume Index	Apical 4C	Unable to assess by 2D TEE
Left Ventricular Ejection Fraction (biplane method)	Apical 4C, 2C, LAX, Parasternal SAX	ME 4C, 2C, LAX, Transgastric SAX
Pulmonary Vein Flow	Apical 4C	ME 2C
E velocity, Deceleration	Apical 4C	ME 4C
e'	Lateral mitral annulus, averaged over 3 beats, Apical 4C	Lateral mitral annulus, averaged over 3 beats, ME 4C
LVOT diameter	Parasternal LAX	ME AV LAX
LVOT VTI (for Stroke Volume)	Apical LAX	Deep gastric LAX

Table 2: Echocardiography data points and their corresponding windows/views for both the TTE and TEE examinations performed.

AV = Aortic Valve; C = Chamber; e' = lateral mitral annular tissue Doppler velocity, LAX = Long Axis View; ME = Midesophageal; SAX = Short Axis View VTI = velocity time integral, LVOT = Left ventricular Outflow Tract, E velocity = Peak mitral early inflow velocity

Study Interventions

After the induction of anesthesia and prior to surgical incision, a TEE probe was inserted into the subjects' esophagus and a CX50 ultrasound machine with an S5-1 sector array transducer probe or IE33 ultrasound machine using an X7-2t matrix array probe (Philips, Philips Healthcare, Andover, MA) was utilized for echocardiography data collection. Intraoperative TEE data points collected are listed in Table 2. The TEE probe was inserted per institutional research TEE protocol. Each subject was analyzed for two main measurements: Doppler derived left ventricular end diastolic pressure (E/e') and

SV/CO using Doppler-derived velocity time integral (VTI) and left ventricular outflow tract (LVOT) diameter.

The E/e' was derived by using the E velocity obtained in the Midesophageal 4 Chamber view (ME 4C) and the e' velocity obtained at the lateral mitral valve annulus also in the ME 4C view. Left ventricular CO was calculated by using the following equations: $\pi r^2 \times \text{LVOT VTI} \times \text{Heart Rate} = \text{left ventricular CO}$ where VTI = the left ventricular VTI and $r = \text{LVOT diameter}/2$. Those values were entered into an electronic data collection form as T₀ (Time zero) Intraoperative TEE.

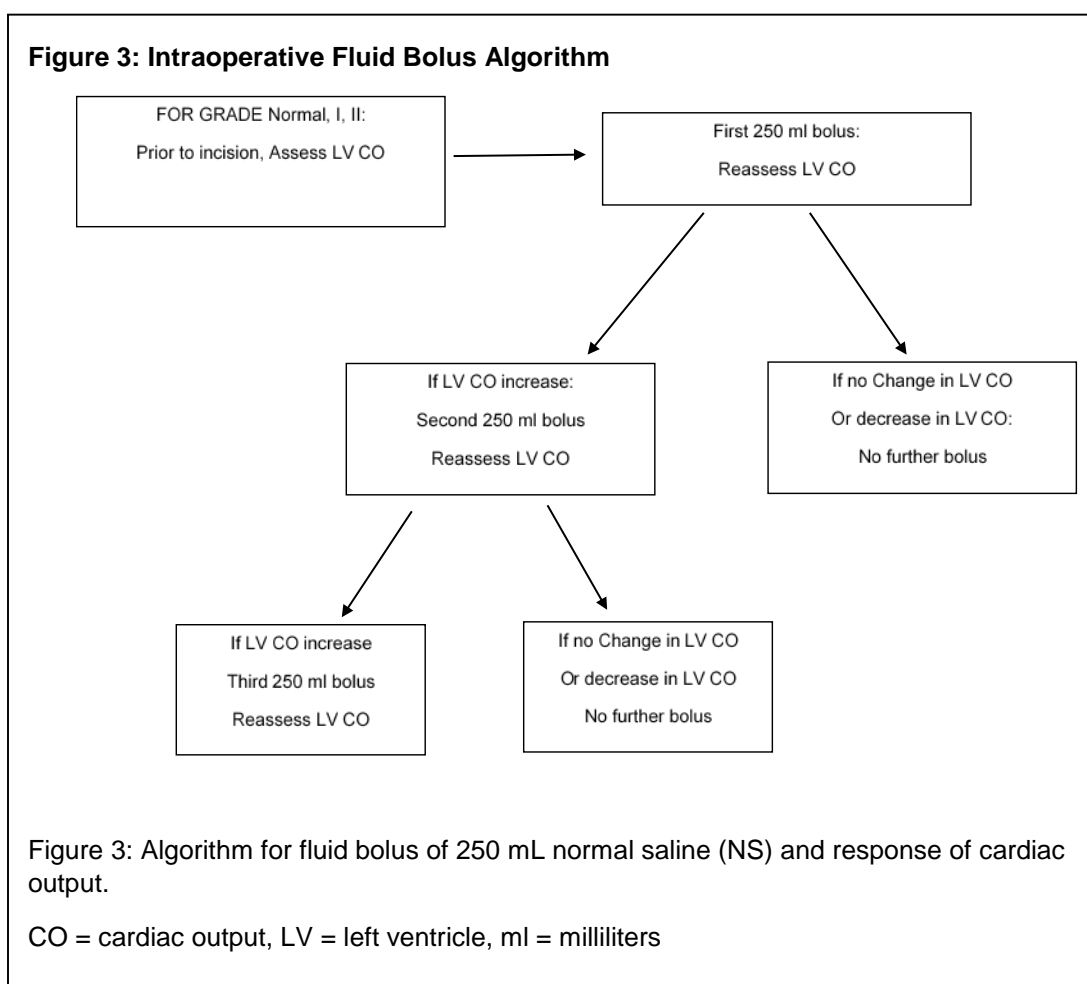
Interventions and Duration

After initial measurements of CO and E/e' were taken, a 250 mL bolus of normal saline (NS) was administered to the subject via a peripheral intravenous catheter for subjects who had normal Grade LVDD, Grade I LVDD, or Grade II LVDD. Subjects with Grade III LVDD were not transfused the bolus of fluid due to risk of pulmonary edema. After the first bolus was complete, repeat measurements of CO and E/e' were taken and documented into the electronic database. It is important to note that while we did not have any patients on screening TEE who had normal LVDD Grade (Grade 0), we had to include Grade 0 in the clinical algorithm, as some subjects theoretically could have a change in LVDD Grade from Grade I to Grade 0 during the perioperative period (as seen in a change from Grade I on screening TTE, for example, to Grade 0 on the Preoperative TTE), as evidenced by our pilot study.

A clinical fluid algorithm was then used based on the subject's change in CO to the initial 250 mL bolus seen in Figure 3. If after one 250 mL bolus there was an increase in CO, a second bolus was administered. If there was no change in CO

or if the CO decrease with fluid bolus administration then no more fluid boluses were given.

After the second 250 mL bolus of NS repeat CO and E/e' measurements were assessed. If after the second 250 mL bolus there an increase in CO, a third and final 250 mL bolus was administered and both CO and E/e' measured and entered in the database as per algorithm listed in Figure 3.



Data Collection

Patient demographics, comorbidities, surgical status and TTE/TEE examination data was collected and placed into an electronic database with the corresponding time interval in which the data was collected. Hemodynamic measurements (blood pressure, pulse, pulse oximeter) were automatically placed into the EMR from the hemodynamic monitor intraoperatively for any further analysis, as were all drugs administered intraoperatively.

Clinical Endpoints

The clinical end points measured are listed below in Table 3. While the intervention was driven on the change in left ventricular CO from fluid bolus, early (E) and late (A) mitral inflow peak velocities, pulmonary vein flow patterns of systolic or diastolic dominance, E/e', and left ventricular ejection fraction were also measured as seen in Table 3.

Table 3: Clinical Endpoints Measured

Demographic	Measurement
Age	
Sex	
BMI	
Race	
Surgical Procedure	
Endpoint	Measurement
Left Ventricular Cardiac Output	$\pi r^2 \times \text{LVOT VTI} \times \text{Heart Rate}$
Peak Early Mitral Inflow Velocity	E
Peak Late Mitral Inflow Velocity	A
Pulmonary Vein Flow Pattern	Systolic or Diastolic Dominant
Left Ventricular Ejection Fraction	EF% by biplane method
Lateral Mitral Annular Tissue Doppler Velocity	e'
LVDD Grade	0, I, II, III

Table 3

BMI = body mass index, LVDD = left ventricular diastolic dysfunction

Data Collected Per Time Period

LVDD Grade, LV CO and E/e' were collected at six different time periods as listed in Figure 4:

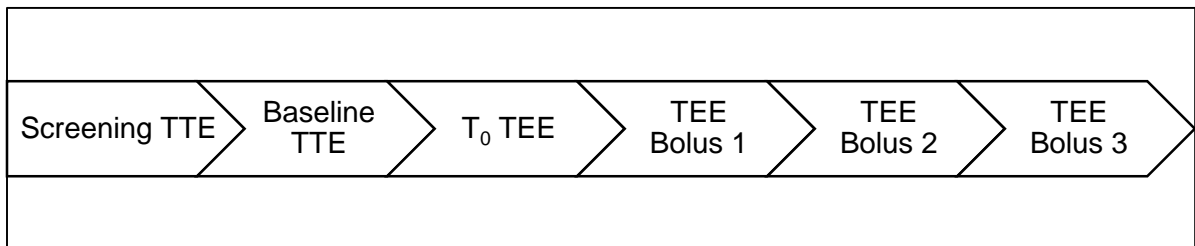


Figure 4. Timeline of echocardiography data points.

TTE=transthoracic echocardiography, TEE=transesophageal echocardiography

- Screening TTE (performed in PASC)
- Baseline TTE (performed day of surgery, prior to induction)
- T₀ TEE (performed after induction of anesthesia, prior to incision)
- TEE Bolus 1 (performed after first 250 mL NS bolus)
- TEE Bolus 2 (performed after first 250 mL NS bolus)
- TEE Bolus 3 (performed after first 250 mL NS bolus)

Statistical Considerations

Descriptive statistics were used to describe patient demographics and changes within LVDD grade. Counts, percentages were used for categorical data and means and standard deviations for continuous data. Side by side box plots were used to show the distribution of LVDD grade, CO, and E/e'.

CHAPTER 3: RESULTS

Seventeen subjects were identified in the PASC that met study criteria and enrolled in the study. One subject voluntarily withdrew from the study during the Preoperative TTE leaving a total number of subjects enrolled=16.

Baseline Characteristics

The average subject age was 74 years. There were 12 (75%) males and 4 females (25%). Average BMI was 26 kg/m². Table 4 lists the subject characteristics, cardiac risk factors and comorbidities. The surgical procedure type is also listed in Table 4.

Table 4: Subject Characteristics, Comorbidities and Surgical Procedure Type

	Study Subjects (N=16) [n (%)] or [Mean (SD)]
Subject Demographics	
• Male Sex	12 (75%)
• Age (years)	74.0 (7.7)
• BMI (kg/m ²)	26 (7.0)
• Race	
Caucasian	15 (94%)
African American	1 (6%)
Cardiac Risk/Comorbidities	
• Hypertension	13 (81%)
• Peripheral Vascular Disease	9 (56%)
• CAD	7 (44%)
• COPD	7 (44%)
• Chronic Kidney Disease	7 (44%)
• Diabetes Mellitus	4 (25%)
• Cerebral Vascular Accident	2 (13%)
Surgical Procedure Type	
• Open AAA Repair	4 (25%)
• EVAR	5 (31%)
• LE Bypass/Repair/Stent	7 (44%)

Table 4: Subject demographics, risk factors and comorbidities and surgical procedure of the N=16 subjects.

AAA=abdominal aortic aneurysm, BMI=body mass index, CAD=coronary artery disease
COPD=chronic obstructive pulmonary disease, EVAR=endovascular aortic repair,
LE=lower extremity, SD=standard deviation

Preoperative Screening TTE Examination

The Preoperative Screening TTE data collected and Grade of LVDD is listed in Table 5. All subjects were found to have evidence of LVDD (Grade I, II) on screening TTE examination. Ten (63%) subjects had Grade I, while six subjects had Grade II (37%). None of the subjects had evidence of LVDD Grade III on screening TTE.

Table 5: Preoperative Screening TTE Data, N=16

Screening TTE Data	N=16 [n (%)] or [Mean (SD)]
Left Ventricular Ejection Fraction (%)	51 (8.04)
Left Ventricular Cardiac Output (L/min)	5.2 (1.7)
e'	8.3 (2.7)
E/e'	10.2 (3.1)
Preoperative Screening Grade of LVDD	
• LVDD Grade I	10 (63%)
• LVDD Grade II	6 (37%)
• LVDD Grade III	-

Table 5: Preoperative screening data from the PASC screening TTE examination.

TTE=transthoracic echocardiogram, E= peak early mitral inflow velocity. e'=lateral mitral annular tissue Doppler velocity, L/min=liters/minute, LVDD=left ventricular diastolic dysfunction

Day of Surgery Baseline TTE Examination

The Preoperative Baseline TTE data collected and Grade of LVDD is listed in Table 6. Fifteen of the 16 subjects were found to have LVDD Grade I [N=12 (75%)] or Grade II [N=3 (19%)] on the preoperative baseline TTE examination the day of surgery. On one of the subjects changed to LVDD Grade I from Grade II on the screening TTE while one subject when from Grade I to normal left ventricular diastolic function the day of surgery when compared to the screening PASC TTE.

Table 6: Preoperative Day of Surgery Baseline TTE Data (N=16)

Baseline TTE Data	N=16 [n (%)] or [Mean (SD)]
Left Ventricular Ejection Fraction (%)	52.5 (5.2)
Left Ventricular Cardiac Output (L/min)	5.1 (2.2)
e'	8.5 (2.3)
E/e'	9.9 (3.3)
Preoperative Screening Grade of LVDD	
• LVDD Normal (Grade 0)	1 (6%)
• LVDD Grade I	12 (75%)
• LVDD Grade II	3 (19%)
• LVDD Grade III	-

Table 6: Preoperative Baseline data from the Day of Surgery baseline TTE examination.

TTE=transthoracic echocardiogram, E= Peak Early Mitral Inflow Velocity. e'=Lateral Mitral Annular Tissue Doppler Velocity, L/min=liters/minute, LVDD=left ventricular diastolic dysfunction

Anesthetic Data

All subjects underwent general anesthesia technique with intravenous induction and maintenance of anesthesia with vapors and narcotics. Saline intravenous flushes in 10 mL syringes were used to push anesthetic drugs for induction to minimize “free-flow” fluid administration. Drugs utilized in study subjects for induction and anesthetic maintenance are listed in Table 7.

Intraoperative TEE Examination (T₀)

Table 7: Anesthetic Drugs Utilized in Study (N=16)

Anesthetic Drug Utilized	N=16
propofol	16 (100%)
fentanyl	15 (94%)
midazolam	13 (81%)
cisatracurium	13 (81%)
sevoflurane	12 (75%)
desflurane	4 (25%)
sufentanil	4 (25%)
rocuronium	3 (19%)

Table 7: Induction and maintenance anesthetic drugs utilized for the study population.

The Intraoperative TEE data collected performed at T₀ (after induction of anesthesia and prior to fluid intervention administration) is listed in Table 8. On initial intraoperative TEE (T₀) 10 subjects had Grade I, four subjects had Grade II, and two subjects had changed to LVDD Grade 0, or had normal appearing diastolic function. No subjects at T₀ had LVDD Grade III.

Table 8: Intraoperative TEE Data T₀ (N=16)

Intraoperative TEE Data	TEE T ₀ N=16	TEE Bolus 1 N=16	TEE Bolus 2 N=7	TEE Bolus 3 N=2
Left Ventricular Ejection Fraction (%)	53 (7.2)	-	-	-
Left Ventricular Cardiac Output (L/min)	4.9 (2.0)	4.6 (1.6)	4.6 (1.5)	5.0 (0.5)
e'	8.8 (2.6)	9.4 (3.1)	8.9 (2.5)	8.0 (2.8)
E/e'	8.7 (4.5)	8.2 (3.9)	7.8 (2.3)	8.5 (2.4)
Preoperative Screening Grade of LVDD				
• LVDD Grade 0 (Normal)	2	1	-	-
• LVDD Grade I	10	9	4	2
• LVDD Grade II	4	6	2	-
• LVDD Grade III	-	-	1	-

Table 8: Intraoperative TEE Data T₀ collected after induction of anesthesia and prior to fluid bolus intervention. After each 250mL bolus of NS, cardiac output and E/e' were calculated and their values recorded per clinical algorithm listed in Figure 3.

TTE=transthoracic echocardiogram, E= Peak Early Mitral Inflow Velocity. e'=Lateral Mitral Annular Tissue Doppler Velocity, L/min=liters/minute, LVDD=left ventricular diastolic dysfunction

Primary Outcome Data

For the entire subject cohort (N=16), the overall CO decreased after Bolus 1 (250 mL) from 4.9 L/min to 4.6 L/min. Nine subjects (9/16, 56%) had no change or a decrease in CO with Bolus 1. Seven subjects (7/16, 44%) had an increase in CO with Bolus 1 and underwent Bolus 2 (250 mL). After Bolus 2, two subjects (N=2/7, 29%) had an increase in CO. A side-by-side boxplot showing the distribution of CO at each of the six time

periods (Screening TTE, Baseline TTE, T₀ TEE, TEE Bolus 1, TEE Bolus 2, and TEE Bolus 3) is noted below in Figure 5.

Figure 5: Left Ventricular Cardiac Output Distribution at Each Time Period

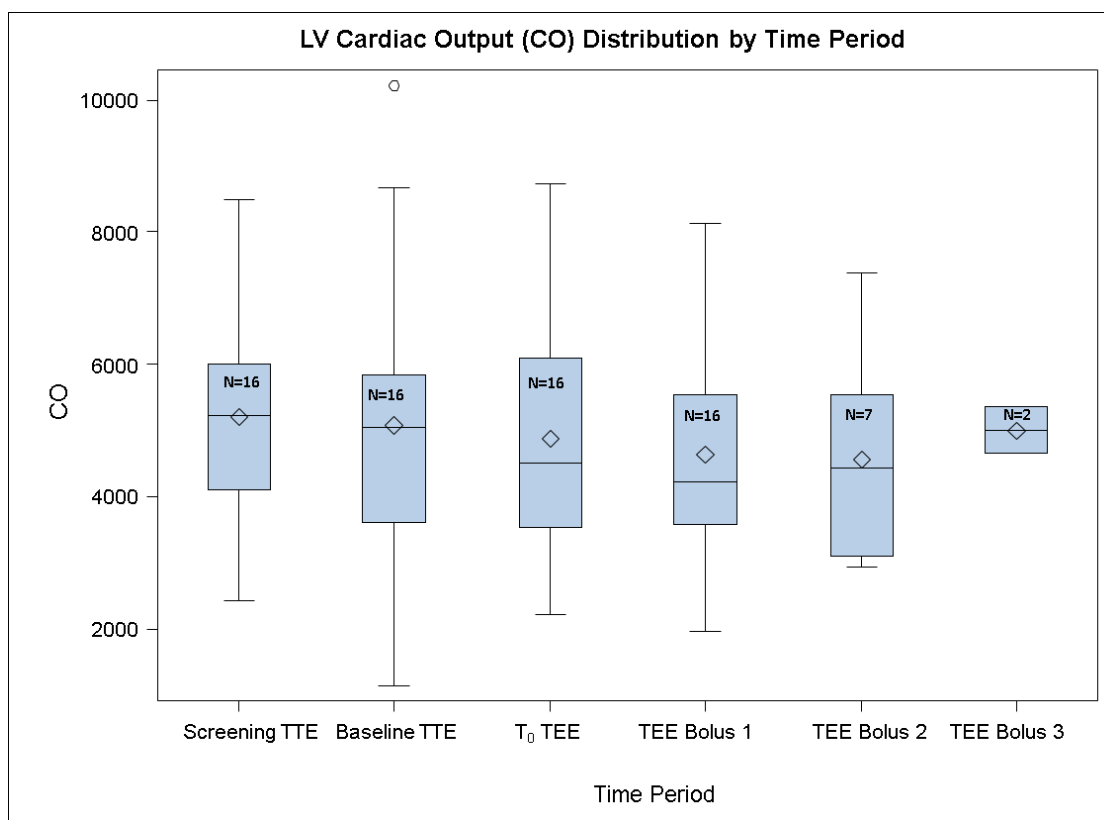


Figure 5: Box Plot depicting the distribution of LV CO at each time period. All subjects (N=16) received the 1st bolus of 250 mL of NS, and then had TEE Bolus 1 data collected. Seven subjects received a 2nd bolus of 250 mL, while only 2 subjects had the 3rd bolus and TEE data collected.

N=subject number, TEE= transesophageal echocardiography, TTE=transthoracic echocardiography, T₀=time zero

Individual patient plots of CO, over each time period, are listed in Figure 6.

Trends at each time period are shown.

Figure 6. Individual Patients CO per Time Period

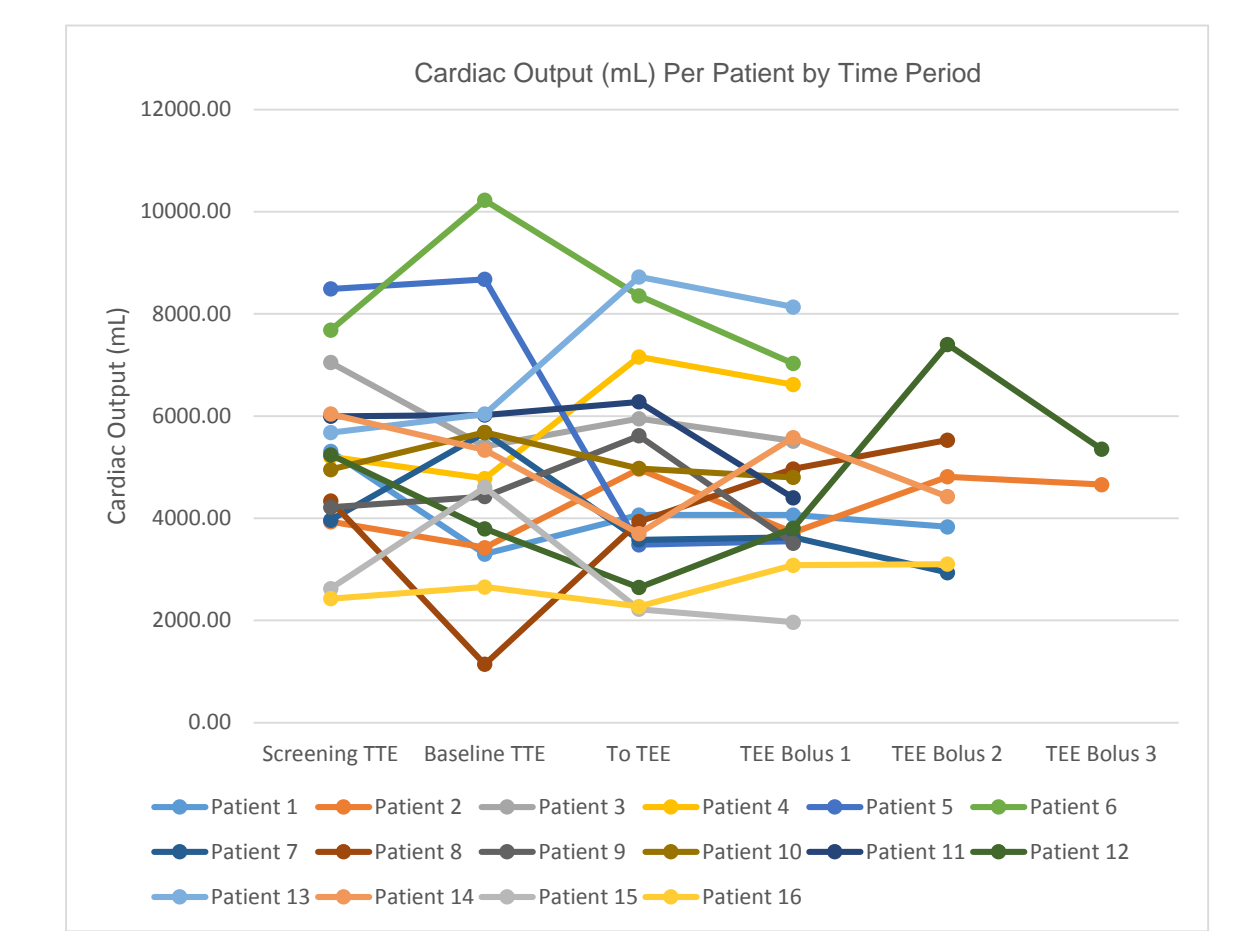


Figure 6: Individual patient's Cardiac Output at each time period.

CO=cardiac output, mL = milliliters, TEE= transesophageal echocardiography, TTE=transthoracic echocardiography, T₀=time zero

Secondary Outcome Data

A side-by-side boxplots showing the distribution of E/e' at each of the six time periods (Screening TTE, Baseline TTE, T₀ TEE, TEE Bolus 1, TEE Bolus 2, and TEE Bolus 3) is listed below in Figure 7. The E/e' decreased from 8.7 to 8.2, while e' increased from 8.8 to 9.5.

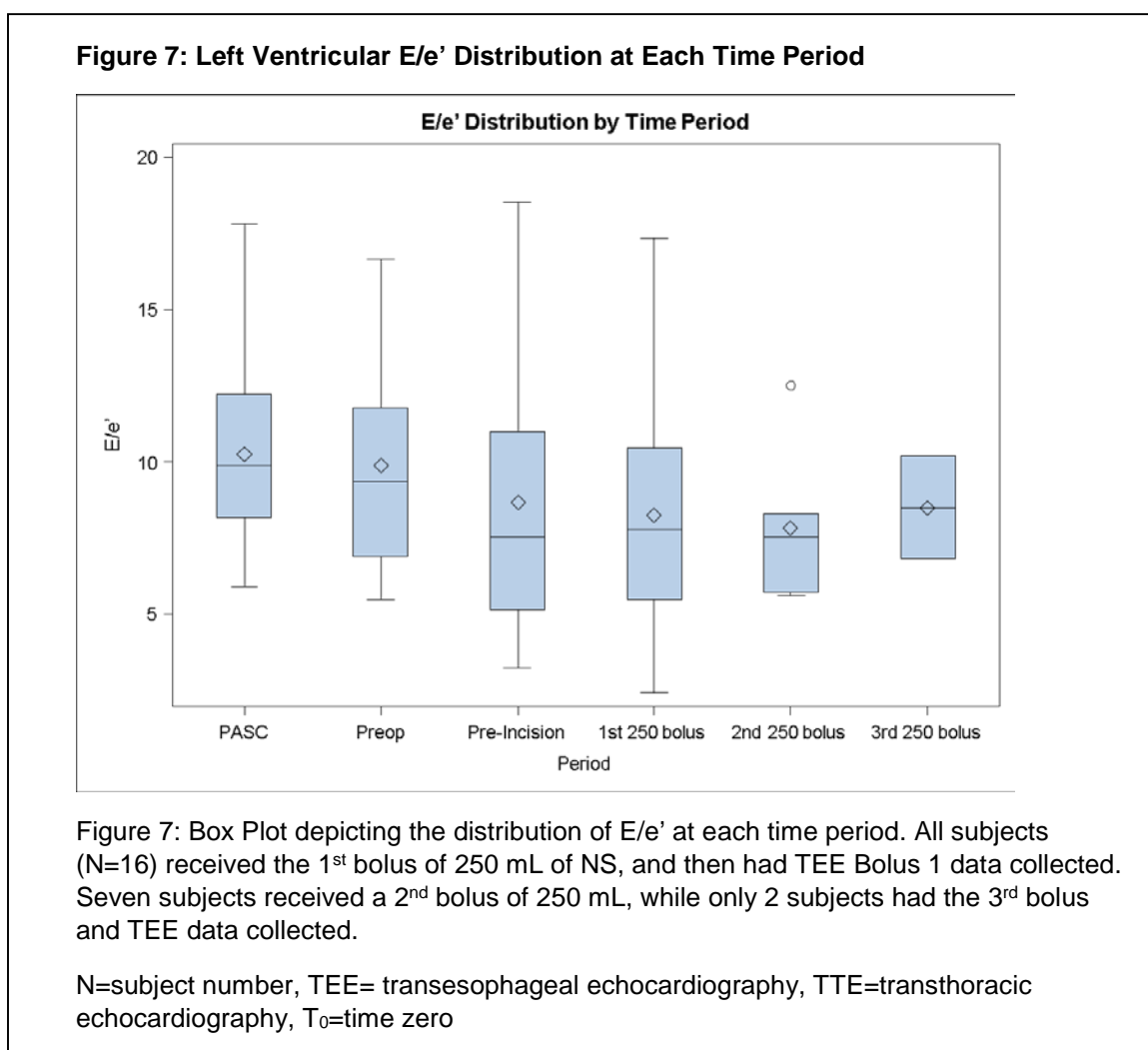


Figure 8 displays Individual patient plots of E/e' over each time period. Trends at each time period are shown.

Figure 8: Individual Patient E/e' per Time Period

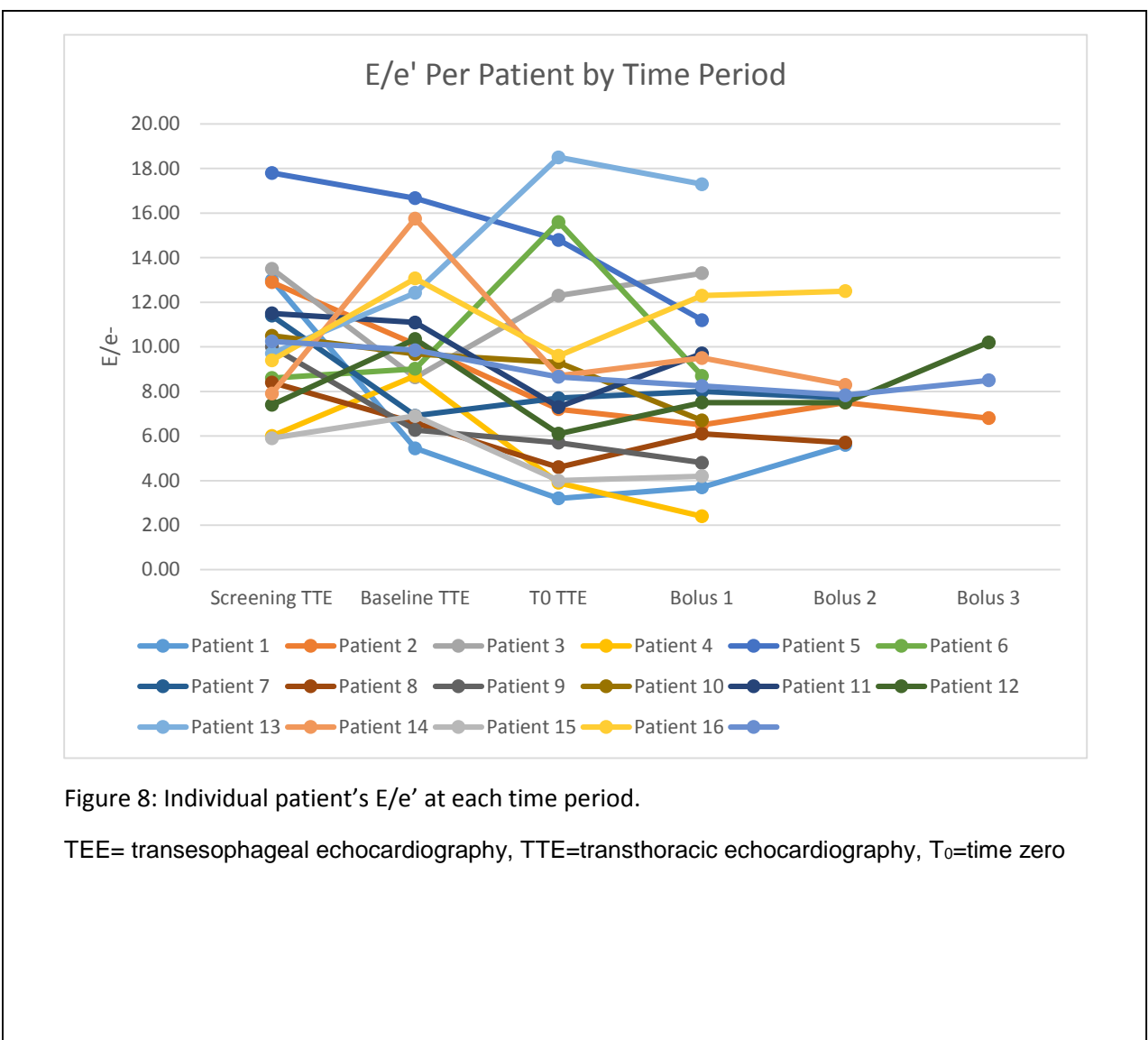


Figure 8: Individual patient's E/e' at each time period.

TEE= transesophageal echocardiography, TTE=transthoracic echocardiography, T₀=time zero

Changes in LVDD Grade

The frequency distribution of LVDD Grade at the six time periods (Screening TTE, Baseline TTE, T₀ TEE, TEE Bolus 1, TEE Bolus 2, and TEE Bolus 3) is displayed below in a clustered bar chart in Figure 9. Five (N=5/16, 31%) subjects had a changes in LVDD Grade after the first bolus.

Figure 9: Left Ventricle Diastolic Dysfunction Grade Distribution at Each Time Period

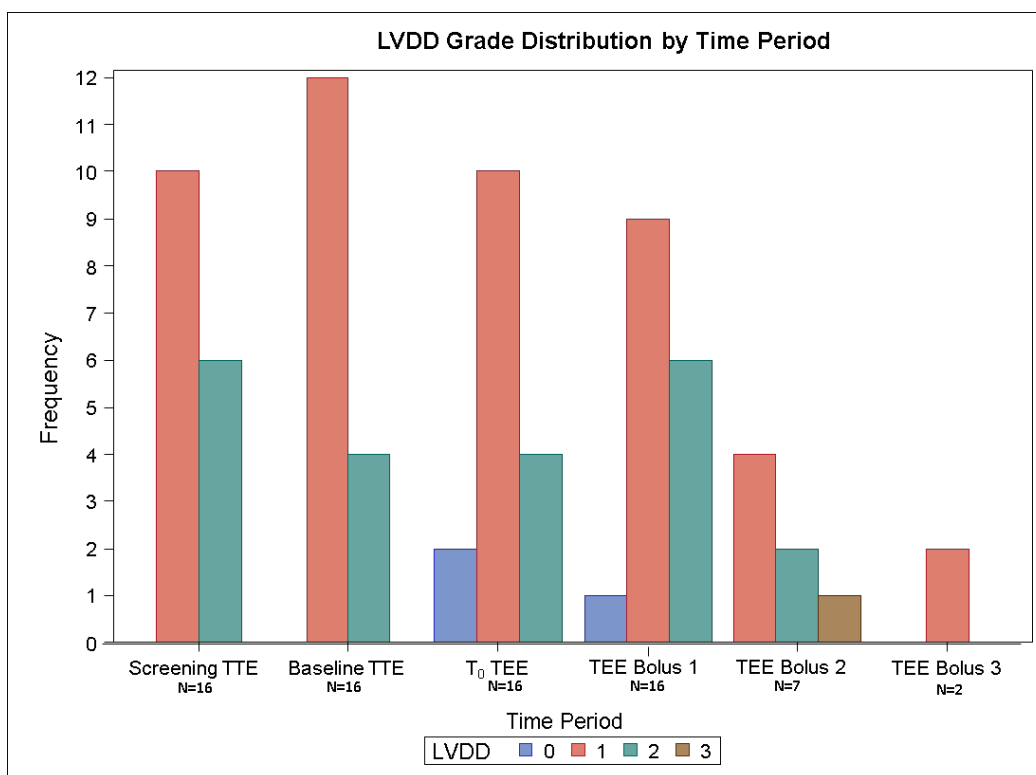


Figure 9: Box Plot depicting the distribution of LVDD Grade at each time period. All subjects (N=16) received the 1st bolus of 250 mL of NS, and then had TEE Bolus 1 data collected. Seven subjects received a 2nd bolus of 250 mL, while only 2 subjects had the 3rd bolus and TEE data collected.

N=subject number, TEE= transesophageal echocardiography, TTE=transthoracic echocardiography, T₀=time zero

Seven subjects had an improvement in CO after the first bolus, and hence then received a second bolus per protocol. The seven subjects who had an improvement in CO, the majority of them (N=5/7,97%) were LVDD Grade I. Two of the subjects were Grade II.

Of those seven subjects, two (N=2/7, 29%) had a change in LVDD Grade after the second bolus. Both of the subjects had an increase in LVDD (one subjects changed from LVDD Grade I to II, while the other went from Grade II to Grade III. Two subjects had an improvement in CO, and received a third bolus of 250 mL NS. One of the two of subjects (N=1/2) changed his/her LVDD Grade from Grade II to Grade I.

Safety Data

There were no adverse events reported with TEE probe insertion or removal or the performance of the TEE. There were no incidences of difficult probe placement or withdrawal. The subjects' medical record was reviewed at hospital discharge and there were no reported oropharyngeal, esophageal or gastric trauma related to the TEE.

CHAPTER 4: DISCUSSION

The primary aim of this study was to evaluate the effect of fluid administration on left ventricular CO in surgical patients with evidence of LVDD. LVDD is risk factor for diastolic heart failure, and perioperative risk is increased for events such CHF and myocardial infarction in patients that have often asymptomatic LVDD.⁷ The direct effects of fluid administration during vascular surgery have not been studied in this population. This study found that in the majority of 16 vascular surgical subjects with LVDD, the administration of fluid boluses did not increase left ventricular CO.

While the administration of fluids is contraindicated in patients that have clinical heart failure, and preclinical evidence of LVDD is a risk for heart failure, perioperatively fluid administration to surgical patients is often warranted due to surgical blood loss, shifts in fluid, and insensible losses. Guidelines and expert recommendations on how to approach fluid administration during the perioperative period for patients that have LVDD are lacking. As such, this study sought to evaluate the effects of fluid in patients with LVDD undergoing vascular surgery with real-time hemodynamic indices such as Doppler derived CO and also left ventricular end-diastolic pressure derived from Doppler echocardiography.

We saw that in 16 elderly surgical subjects with LVDD, there was a trend that 250 mL fluid boluses did not increase CO in nine of 16 of patients. In patients who did have a rise in CO with the fluid bolus, they were more likely to have LVDD Grade I and normal Doppler-derived left-sided filling pressures. This would support idea that in patients with LVDD Grade I, LV filling pressures are likely normal, and the risk of developing CHF or diastolic heart failure may be lower than in patients with higher grade of LVDD and higher left-sided filling pressures. As such, a more liberal approach to

administration of perioperative fluids may be less likely to cause postoperative adverse events such as heart failure. Preoperative screening of patients and classification of LVDD Grade may provide information to guide anesthesiologists on perioperative fluid administration decisions. In the perioperative arena, where fluid boluses are often required and necessary, some patients with LVDD Grade I may respond to fluid challenges with an improvement in LV CO as suggested by this pilot data. Whereas patients that have advanced stages of LVDD, such as LVDD Grade II or III, may not see this benefit. As such, the risk/benefit analysis of fluid administration to this population needs to be analyzed with future outcome studies.

The second aim of the study was to evaluate if and how fluid boluses changed E/e' , or Doppler-derived filling pressures, in subjects with LVDD Grade II and Grade III. We saw a trend that moderate fluid boluses did not change E/e' , they may change LVDD Grades. For example, after the first 250mL bolus, we found 4 subjects (N=4/16, 25%) demonstrated an increase in their LVDD Grade, suggesting an increase in LV filling pressures. This was also demonstrated in two subjects (N=2/7, 29%) who qualified for a second fluid bolus of 250mL. While 5 subjects demonstrated no change in LVDD Grade, two subjects demonstrated a worsening LVDD Grade. While this section of the study was not powered to evaluate clinical outcomes, previous studies have demonstrated that patients with worsening LVDD Grade have worse clinical outcomes.^{4,7,8} A further study evaluating the change in subjects LVDD grade that is powered to demonstrate a correlation with an increase in adverse outcomes is currently underway.

This second aim provides more insight into the direct effects of fluid administration to two often coupled indices: E/e' , or Doppler-derived LV filling pressure (LVEDP), and LVDD Grade. While we know these two measurements are directly

proportional, whereas an increase in E/e' theoretically leads to an increase in LVDD Grade, there seems to be more to this relationship than a pure linear association. As E/e' is a continuous variable versus LVDD Grade being categorical (0, I, II, III), it can be extrapolated that there will be changes in LVDD Grade, which has been historically derived from mitral inflow velocity patterns and pulmonary vein flow velocity patterns which may or may not be reflected in E/e' , which is derived from both mitral inflow velocity and tissue-Doppler velocity. The fact that fluid boluses were found to result in a worsening of LVDD Grade in some subjects but did not result in a significant change in E/e' suggests that these indices may reflect different physiological changes. The differences in response to fluid boluses between these two indices may be better explained by the effect of the loading conditions, whereas mitral inflow velocities and pulmonary vein flow velocities are more load-dependent, where e' is well understood to be less dependent on loading conditions.^{5,16} Which of these indices do in fact change more with fluid administration, and whether those changes are tied to differences in clinical outcomes, is part of the adjunct clinical trial underway.

The findings in this study, similar to our preliminary study, demonstrate the dynamic and sensitive nature of LVDD Grade.²⁵ The Grade of LVDD, which has been traditionally determined by mitral inflow patterns and pulmonary vein flow patterns and tissue Doppler velocity of the mitral annulus, can change with loading conditions during the perioperative period, as shown in our pilot study and repeated in this study. The fact that LVDD Grade can change with fluid administration begs one to wonder if anesthesiologists who administer perioperative fluids to high-risk patients can optimize fluid administration, resulting in optimizing LVDD Grade and LV CO. And if anesthesiologists can optimize fluids based on a patient's baseline LVDD Grade, does this lead to an optimization of postoperative outcomes?

Vascular surgical patients, most of which are elderly, present a special set of challenges to the anesthesiologist. Risk factors such as hypertension, advanced age, coronary artery disease (CAD), and renal dysfunction are common in the vascular surgical population. Arterial hypertension and higher baseline perfusion pressures, along with reperfusion injury associated with the cross-clamping and release of major vasculature during surgery make it very challenging for the anesthesiologist to maintain adequate organ perfusion and avoid post-operative organ failure.³⁵ Optimizing fluid management is very important to perioperative organ perfusion.³⁶ The disruption of the capillary barrier, from either hypovolemia or hypervolemia, is associated with poor outcomes, leading to current investigations to suggest GDT may lead to improved postoperative outcomes in major surgery.^{36,37}

GDT, targeted at providing euolemia and avoidance of excess salt and water, plays an important part of improving outcomes in major surgery and in high risk patients, who often have a hard time excreting water and/or salt due to comorbidities. But what is GDT in patients with LVDD? This study adds to the first step in defining GDT in this population.

The previous mantra of “filling the third space” has been disbanded as this space does not exist physiologically.^{35, 36,37,38} However, for the last century, the doctrine of filling the third space, a “hidden” area within the body thought to consume volume in perioperative patients, has been perpetuated from generation to generation of physicians. Despite our recent knowledge that this space does not exist, trends in fluid administration illustrate that many clinicians still practice liberal fluid practices based on this theory, institutional preferences, and surgical tendencies.²⁷ Intraoperative insensible losses, once thought to require maintenance fluid replacement as high as 10-20

mg/kg/hour, are now known to be much lower, and 0.5-1 mg/kg/hour is the accepted replacement therapy to avoid capillary leak and interstitial edema.^{35,36,37} In order to optimize fluid management, GDT has recently been adopted, where fluid administration is based on physiological needs and hemodynamic data such as SV. While GDT has been shown to be beneficial in many surgical arenas, it is not practiced in most institutions. The institution of GDT into perioperative practice has been limited due requirements of a focused evaluation of hemodynamic measurements such as SV or CO, which many institutions lack the resources to fulfill. Current studies in major abdominal surgery have shown that fluid protocols and algorithms supporting GDT are associated with improved outcomes.^{36,39} Recent meta-analyses and reviews suggest it is not the type or amount of fluid that is most important, but rather following a protocol based on hemodynamic data.³⁹

SV is considered to be the gold standard for measuring a patient's response to fluid and where the patient is on the Frank-Starling curve.^{30,36,40} Once a patient is euvolemic, administration of fluid will result in a <10% change in SV and assumed to be on the plateau of the Frank-Starling curve.⁴¹ While GDT using SV is invaluable, it requires training and expertise not available to all patients. While not every patient undergoing vascular surgery may have GDT using SV, the establishment of guidelines and recommendations to optimize fluid management for this population may be beneficial to shift the current paradigms. As this study revealed, changes in LVEDP and SV/CO with fluid boluses may not be as predictable in the patients with LVDD. Vascular surgery, unlike major abdominal surgery, has its own set of challenges for euvolemia that may make GDT even more helpful in this population and higher risk surgical procedure.

Can perioperative fluid algorithms optimize hemodynamics and outcomes in patients with LVDD undergoing vascular surgery? The answer to this question has not been studied. While general preventative practices to avoid diastolic heart failure in patients with LVDD exist, we do not know how to avoid diastolic heart failure in surgical patients with LVDD, many of which undergo vascular surgery. This study is the first study to measure SV and CO response to fluid boluses in high-risk patient undergoing vascular surgery. While heart rate and mean arterial pressure are the traditional mainstay of clinicians to determine response to fluid, they are poor estimates of true circulating blood volume and hypovolemia. A meta-analysis by Marik and colleagues found that only 50% of patients who are hemodynamically unstable are fluid responders.⁴¹ In vascular surgical patients, fluid optimization is critical. Clamping and unclamping of the aorta and major vessels, reperfusion of organs, potential for hemorrhage, and protection of organs require significant fluid management during the surgical period. High risk patients with vascular disease and cardiac comorbidities require a focused approach to fluid optimization during vascular surgery, where diseases such as LVDD can complicate fluid requirements. Understanding the patient's physiological response to fluids and the risk associated with under or over hydration is arguably one of the most difficult yet important tasks to the anesthesiologist. Understanding how left ventricular filling pressure and SV change in response to over and under hydration is the first step to defining this important task.

Future studies are warranted to assess the need for GDT, how GDT is defined, and how and if GDT changes outcomes in vascular surgical patients. Anesthesiologists are the gatekeepers of perioperative fluid management. Dissemination of target goals and the definition of GDT to promote enhanced recovery after vascular surgery are needed to improve anesthetic care of the elderly population who have LVDD.

BIBLIOGRAPHY

¹Goodney PP, Beck AW, Nagle J, Welch G, Zwolak RM. National trends in lower extremity bypass surgery, endovascular interventions, and major amputations. *J of Vasc Surg* 50:54-60, 2009.

²Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: part 1: diagnosis, prognosis, and measurements of diastolic function. *Circulation* 105:1387-93, 2002

³Hammill BG, Curtis LH, Bennett-Guerrero E, O'Connor CM, Jollis JG, Schulman KA, Hernandez AF. Impact of heart failure on patients undergoing major noncardiac surgery. *Anesthesiology* 108:559-67, 2008

⁴Redfield MM, Jacobsen SJ, Burnett JC, Mahoney DW, Bailey KR, Rodeheffer RJ. Burden of systolic and diastolic ventricular dysfunction in the community: appreciating the scope of the heart failure epidemic. *JAMA* 289:194-202, 2003

⁵Matyal R, Skubas NJ, Shernan SK, Mahmood F. Perioperative assessment of diastolic dysfunction. *Anesth Analg* 113:449-72, 2011

⁶Dunlay SM, Shah ND, Shi Q, Morlan B, VanHouten H, Long KH, Roger VL. Lifetime costs of medical care after heart failure diagnosis. *Circ Cardiovasc Qual* 4:68-75, 2011

⁷Flu WJ, van Kuijk JP, Hoeks SE, Kuiper R, Schouten O, Goei D, Elhendy A, Verhagen HJ, Thomson IR, Bax JJ, Fleisher LA, Poldermans D. Prognostic implications of asymptomatic left ventricular dysfunction in patients undergoing vascular surgery. *Anesthesiology* 112:1314-24, 2010

-
- ⁸ Matyal R, Hess PE, Subramaniam B, Mitchell J, Panzica PJ, Pomposelli F, Mahmood F. Perioperative diastolic dysfunction during vascular surgery and its association with postoperative outcome. *J Vasc Surg* 50:70-6, 2009
- ⁹ Sandham JD, Hull RD, Brant RF, Knox L, Pineo GF, Doig CJ, Laporta DP, Viner S, Passerini L, Devitt H, Kirby A, Jacka M. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *NEJM* 348:5-14, 2003.
- ¹⁰ Skubas N. Intraoperative Doppler tissue imaging is a valuable addition to cardiac anesthesiologists' armamentarium: a core review. *Anesth Anal* 108:48-66, 2009
- ¹¹ Groban L, Sanders DM, Houle TT, Antonio BL, Ntuen EC, Zvara DA, Kon ND, Kincaid EH. Prognostic value of tissue Doppler-derived E/e' on early morbid events after cardiac surgery. *Echocardiography* 27:131-8, 2010
- ¹² Shah MR, Hasselblad V, Stevenson LW, Binanay C, O'Connor CM, Sopko G, Califf RM. Impact of the pulmonary artery catheter in critically ill patients. *JAMA* 294:1664-70, 2005.
- ¹³ Centers for Disease Control: Database: Rate of all-listed procedures for discharges from short-stay hospitals by procedure category and age: United States, 2009. Accessed August 15, 2012
- ¹⁴ AlJaroudi W, Alraies MC, Halley C, Rodriguez L, Grimm RA, Thomas JD, Jaber WA. Impact of progression of diastolic dysfunction on mortality in patients with normal ejections fractions. *Circulation* 125:782-8, 2012
- ¹⁵ Swaminathan M, Nicoara A, Phillips-Bute BG, Aeschlimann N, Milano CA, Mackensen GB, Podgoreanu MV, Velazquez EJ, Stafford-Smith M, Mathew JP. Utility of a simple

algorithm to grade diastolic dysfunction and predict outcome after coronary artery bypass graft surgery. *Ann Thorac Surg* 91:1844-51, 2011

¹⁶ Nageuh SF, Appleton CP, Gillebert TC, Marino PN, Oh JK, Smiseth OA, Waggoner AD, Flachskampf FA, Pellikka PA, Evangelista A. Recommendations for the evaluation of left ventricular diastolic function by echocardiography. *JASE* 22:107-28, 2009

¹⁷ Phillip B, Pastor D, Bellows W, Leung JM. The prevalence of preoperative diastolic filling abnormalities in geriatric surgical patients. *Anesth Analg* 97:1214-21, 2003

¹⁸ Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Alteration of left ventricular diastolic function by desflurane, isoflurane, and halothane in the chronically instrumented dog with autonomic nervous system blockade. *Anesthesiology* 74:1103-14, 1991

¹⁹ Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Reversal of volatile anesthetic-induced depression of myocardial contractility by extracellular calcium also enhances left ventricular diastolic function. *Anesthesiology* 78:141-54, 1993

²⁰ Pagel PS, Kampine JP, Schmeling WT, Warltier DC. Alteration of canine left ventricular diastolic function by intravenous anesthetics in vivo: ketamine and propofol. *Anesthesiology* 76:419-25, 1992

²¹ Van Diepen S, Bakal JA, McAlister FA, Ezekowitz JA. Mortality and readmission of patients with heart failure, atrial fibrillation or coronary artery disease undergoing noncardiac surgery: an analysis of 38047 patients. *Circulation* 124:289-96, 2011

²² Grocott MP, Mythen MG, Gan TJ. Perioperative fluid management and clinical outcomes in adults. *Anesth Analg* 100:1093-106, 2005

²³ Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einay S, Matot I. Effect of

intraoperative fluid management on outcome after intrabdominal surgery.

Anesthesiology 103:25-32, 2005

²⁴ Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg* 112:640-51, 2012

²⁵ Shillcutt SK, Montzingo CR, Agrawal A, Khaleel MS, Therrien SL, Thomas WR, Porter TR, Brakke TR. Echocardiography-based hemodynamic management of left ventricular diastolic dysfunction: a feasibility and safety study. *Echocardiography* 31:1189-1198, 2014.

²⁶ Navarro LH, Bloomstone JA, Auler JO, Cannesson M, Rocca GD, Gan TJ, Kinsky M, Magder S, Miller TE, Mythen M, Perel A, Reuter DA, Pinsky MR, Kramer GC.

Perioperative fluid therapy: a statement from the international fluid optimization group.

Perioper Med (Lond) 4:1-20, 2015

²⁷ Lilot M, Ehrenfeld JM, Lee C, Harrington B, Cannesson M, Rinehart J. Variability in practice and factors predictive of total crystalloid administration during abdominal surgery: retrospective two-centre analysis. *Br J Anaesth* 114:767-76, 2015

²⁸ Thacker JK, Mountford WK, Ernst FR, Kruk MR, Mythen MM. Perioperative fluid utilization variability and association with outcomes: consideration for enhanced recovery efforts in sample US surgical populations. *Ann Surg* 263:502-510, 2016

²⁹ Minto G, Mythen MG. Perioperative fluid management: science, art, or random chaos? *Br J Anaesth* 2015;114:717-21

³⁰ Ansari et al. Physiological controversies and methods used to determine fluid responsiveness: a qualitative systemic review. *Anaesthesia* 71:94-105, 2016

-
- ³¹ Ferrari R, Bohm M, Cleland JGF, Paulus WJS, Pieske B, Rapezzi C, Tavazzi L. Heart failure with preserved ejection fraction: uncertainties and dilemmas. *Eur J Heart Failure* 17:665-671, 2015.
- ³² Munzel T, Gori Tommaso, Keaney Jr JF, Maack C, Daiber A. Pathophysiological role of oxidative stress in systolic and diastolic heart failure and its therapeutic implications. *Euro Heart J* 36:2555-64, 2015
- ³³ Das A, Abraha S, Deswal A. Advances in the treatment of heart failure with preserved ejection fraction. *Curr Opin Cardiol* 23:233-40, 2008
- ³⁴ Butler J, Fonarow GC, Zile MR, Lam CS, Roessig L, Schelbert EB, Shah SJ, Ahmed A, Bonow RO, Cleland JGF, Cody RJ, Chioncel O, Collins SP, Dunmon P, Filippatos G, Lefkowitz MP, Mari CN, McMurray JJ, Misselwitz F, Nodari S, O'Connor C, Pfeffer MA, Pieske B, Pitt B, Rosano G, Sabbah HN, Senni M, Solomon SD, Stockbridge N, Teerlink JR, Georgiopolou W, Gheorghiade M. Developing therapies for heart failure with preserved ejection fraction: current state and future directions. *JACC Heart Fail* 2:97-112, 2014
- ³⁵ Jacob M, Chappell D, Hollmann MW. Current aspects of perioperative fluid handling in vascular surgery. *Curr Opin Anaesthesiol* 22:100-108, 2009
- ³⁶ Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to enhanced recovery after surgery (ERAS). *Can J Anesth* 62:158-168, 2015
- ³⁷ Gupta R, Gan TJ. Perioperative fluid management to enhance recovery. *Anaesthesia* 71:40-45, 2016
- ³⁸ Jacob M, Chappell D, Rehm M. The 'third' space – fact or fiction. *Best Pract Res Clin Anaesth* 23:145-147, 2009
- ³⁹ Pearse RM, Harrison DA, MacDonald N, Gillies MA, Blund M, Ackland G, Grocott, MPW, Ahern A, Griggs K, Scott R, Hinds C, Rowan K. Effect of a perioperative cardiac

output-guided hemodynamic therapy algorithm on outcomes following major gastrointestinal surgery: a randomized clinical trial and systemic review. *JAMA* 311:2181-2190, 2014

⁴⁰ Cecconi M, Parsons AK, Rhodes A. What is a fluid challenge? *Curr Opin Crit Care* 17:290-295, 2011

⁴¹ Marik PE, Cavallazzi R. Does the central venous pressure predict fluid responsiveness? An updated meta-analysis and a plea for some common sense. *Crit Care Med* 41:1774-1781, 2013

APPENDIX

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ADULT CONSENT - CLINICAL BIOMEDICAL

Title of this Research Study

Echocardiography-Guided Hemodynamic Management Strategy to Improve Clinical Outcomes for Elderly Patients with Left Ventricular Diastolic Dysfunction Undergoing Noncardiac Surgery

Invitation

You are invited to take part in this research study. You have a copy of the following, which is meant to help you decide whether or not to take part:

- Informed consent form
- "What Do I need to Know Before Being in a Research Study?"
- The Rights of Research Subjects

Why are you being asked to be in this research study?

You are being asked to be in this research study because you are scheduled to undergo a major non-heart surgery at the University of Nebraska Medical Center, and you are 60 years of age or older.

A total of 200 patients will be enrolled in the study.

What is the reason for doing this research study?

The purpose of this research is to see if echocardiography (a sound wave picture of the heart) during surgery can help the doctor who gives the sedation medication (Anesthesiologist) better manage fluid levels and medications during the surgery, and reduce the chance of complications during and after the surgery

What will be done during this research study?

You will be randomly assigned (like the flip of a coin) to one of two groups before your surgery. An equal number of patients will be assigned to each research group. Subjects who do not have stiffening of the large chamber located on the left side of the heart (Left Ventricular Dysfunction) also known as LVDD, seen on echocardiogram completed prior to surgery, will be withdrawn from the study.

All subjects will have an echocardiogram before surgery. This involves placing a probe on your chest and taking sound wave pictures of your heart through

your chest. After you are asleep for the surgery, you will have a different echocardiogram probe placed through your mouth into your esophagus, by the anesthesia doctor. This will take sound wave pictures of your heart during the entire operation. The probe will be removed before you wake up.

If you are in the EXPERIMENTAL group, the anesthesia doctor will adjust how he gives you IV fluids, or blood pressure medicines, based on the measurements from the pictures of your heart from the echocardiogram.

If you are in the STANDARD group, you will be treated as if you weren't in the research. The IV fluids or blood pressure medicines you get during the operation will be based on the anesthesia doctor's judgment, based on your heart rate, blood pressure and physical examination.

All subjects will have data collected including: clinical outcomes (heart failure, atrial fibrillation, arrhythmia, or other cardiac complications), blood draws, length of stay (hospital or Intensive Care Unit), readmission to the Hospital for a cardiac event (heart attack, A-fib, congestive heart failure, or death) at 30 or 90 days, new diagnosis of Acute Kidney Injury. All data will be collected from your medical record; however, if no records are available, you may receive a phone call to ensure that you have not been treated at a hospital other than UNMC. If you are treated within 30 days of your surgery, outside of UNMC, the study team will have your permission to collect those medical records

What are the possible risks of being in this research study?

The risks associated with the Echocardiography Guided Hemodynamic Management (EGHEM) study can be related to direct injury or trauma from the probe that goes down your throat to look at your heart (transesophageal echocardiography (TEE)) probe, or from mismanagement of fluid and/or drug administration during surgery. The risks from direct TEE probe trauma include damage or tears to the throat, water being pushed in to the lungs and dental trauma. The risks from mismanagement of fluid and/or drug administration include acute heart attacks, abnormal fluid build-up in the lungs, kidney failure, orthostatic hypotension (low blood pressure when changing position) and/or death.

It is possible that other rare side effects could occur which are not described in this consent form. It is also possible that you could have a side effect that has not occurred before.

What are the possible benefits to you?

You may benefit if you are randomized to the experimental group, and the experimental group is found to be better than the standard group, which may reduce your post-operative complications association with your heart. However, you may not get any benefit from being in this research study.

What are the possible benefits to other people?

Possible benefits to society are an advancement in medical knowledge in the management of future patients with heart disease during major surgery.

What are the alternatives to being in this research study?

Instead of being in this research study, you can choose not to participate.

What will being in this research study cost you?

There is no cost to you to be in this research study.

Will you be paid for being in this research study?

You will not be paid to be in this research study.

Who is paying for this research?

This research is being paid for by grant funds from the National Institute of Health (NIH) and the American Society of Geriatrics. UNMC/TNMC receives money from the NIH to conduct this study.

What should you do if you are injured or have a medical problem during this research study?

Your welfare is the main concern of every member of the research team. If you are injured or have a medical problem as a direct result of being in this study, you should immediately contact one of the people listed at the end of this consent form. Emergency medical treatment for this injury or problem will be available at the Nebraska Medical Center. If there is not sufficient time, you should seek care from a local health care provider.

UNMC/TNMC has no plans to pay for any required treatment or provide other compensation. If you have insurance, your insurance company may or may not pay the costs of medical treatment. If you do not have insurance, or if your insurance company refuses to pay, you will be expected to pay for the medical treatment.

Agreeing to this does not mean you have given up any of your legal rights.

How will information about you be protected?

You have rights regarding the protection and privacy of your medical information collected before and during this research. This medical information is called "protected health information" (PHI). PHI used in this study may include your medical record number, address, birth date, medical history, the results of physical exams, blood tests, x-rays as well as the results of other diagnostic medical or research procedures. Only the minimum amount of PHI will be collected for this research. Your

research and medical records will be maintained in a secure manner.

Who will have access to information about you?

By signing this consent form, you are allowing the research team to have access to your PHI. The research team includes the investigators listed on this consent form and other personnel involved in this specific study at the Institution.

Your PHI will be used only for the purpose(s) described in the section What is the reason for doing this research study?

You are also allowing the research team to share your PHI, as necessary, with other people or groups listed below:

- ◆ The UNMC Institutional Review Board (IRB) Institutional officials designated by the
- ◆ UNMC IRB
- ◆ Federal law requires that your information may be shared with these groups: The HHS Office for Human Research Protections (OHRP)

National Institutes of Health (NIH)

You are authorizing us to use and disclose your PHI for as long as the research study is being conducted.

You may cancel your authorization for further collection of PHI for use in this research at any time by contacting the principal investigator in writing. However, the PHI which is included in the research data obtained to date may still be used. If you cancel this authorization, you will no longer be able to participate in this research.

How will results of the research be made available to you during and after the study is finished?

In most cases, the results of the research can be made available to you when the study is completed, and all the results are analyzed by the investigator or the sponsor of the research. The information from this study may be published in scientific journals or presented at scientific meetings, but your identity will be kept strictly confidential.

If you want the results of the study, contact the Principal Investigator at the phone number given at the end of this form or by writing to the Principal Investigator at the following address:

Sasha K Shillcutt, MD

University of Nebraska Medical Center

981145 Nebraska Medical Center Omaha, NE 68198-1145

A description of this clinical trial will be available on www.ClinicalTrials.gov, as required by U.S. law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What will happen if you decide not to be in this research study?

You can decide not to be in this research study. Deciding not to be in this research will not affect your medical care or your relationship with the investigator or UNMC/TNMC. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

What will happen if you decide to stop participating once you start?

You can stop participating in this research (withdraw) at any time by contacting the Principal Investigator or the Lead Coordinator by phone, or you may also contact one of these individuals in writing at the following address:

Sasha K Shillcutt, MD

University of Nebraska Medical Center 981145 Nebraska Medical Center Omaha, NE 68198-1145

Deciding to withdraw will otherwise not affect your care or your relationship with the investigator or UNMC/TNMC. You will not lose any benefits to which you are entitled.

For your safety, please talk to the research team before you stop taking any study drugs or stop other related procedures. They will advise you how to withdraw safely. If you withdraw you may be asked to undergo some additional tests. You do NOT have to agree to do these tests.

Any research data obtained to date may still be used in the research.

Will you be given any important information during the study?

You will be informed promptly if the research team gets any new information during this research study that may affect whether you would want to continue being in the study.

What should you do if you have any questions about the study?

You have been given a copy of "*What Do I Need to Know Before Being in a Research Study?*" If you have any questions at any time about this study, you should contact the Principal Investigator or any of the study personnel listed on this consent form or any other documents that you have been given.

What are your rights as a research participant?

You have rights as a research subject. These rights have been explained in this consent form and in *The Rights of Research Subjects* that you have been given. If you have any questions concerning your rights or complaints about the research, you can contact any of the following:

- ◆ The investigator or other study personnel Institutional Review Board (IRB)
- ◆ Telephone: (402) 559-6463 Email: IRBORA@unmc.edu
Mail: UNMC Institutional Review Board, 987830 Nebraska Medical Center, Omaha, NE 68198-7830
- ◆ Research Subject Advocate Telephone: (402) 559-6941 Email: unmcrsa@unmc.edu

Documentation of informed consent

You are freely making a decision whether to be in this research study. Signing this form means that:

- ◆ You have read and understood this consent form. You have had the consent form explained to you.
- ◆ You have been given a copy of *The Rights of Research Subjects* You have had your questions answered.
- ◆ You have decided to be in the research study.
- ◆ If you have any questions during the study, you have been directed to talk to one of the investigators listed below on this consent form.
- ◆ You will be given a signed and dated copy of this consent form to keep.

Signature of Subject _ Date _

My signature certifies that all the elements of informed consent described on this consent form have been explained fully to the subject. In my judgment, the subject possesses the legal capacity to give informed consent to participate in this research and is voluntarily and knowingly giving informed consent to participate.

Signature of Person obtaining consent _____

Date __

Authorized Study Personnel Principal

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