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The Use of Transesophageal Echocardiography for the Assessment of Left Ventricular
Volume and Function in Patients Undergoing Acute Normovolemic Hemodilution as a Human
Hemorrhagic Model

by

David D. Rose

DISSERTATION

Submitted in partial satisfaction of the requirements for the degree of

DOCTOR OF PHILOSOPHY

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GRADUATE DIVISION

of the

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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By
David D. Rose

Dedication and Acknowledgments

This doctoral “journey” has been a successful endeavor because of the help and encouragement of so many colleagues, friends, and family who supported me in countless different ways. First of all, I would like to dedicate this work to the memory of my parents, who taught me the value of an education and that one was never too old to learn. It was their early words of wisdom and fond memories that helped me throughout these last six years.

This educational process would not have been possible without the strong collegial bonds that I am fortunate to have made among the department’s nurse anesthetists and anesthesiologists over the past twenty-three years at the UC Davis Medical Center. I owe a special debt of gratitude to Dr. Peter Moore, the Chair of the Department of Anesthesiology and Pain Medicine, for his unwavering support during the past six years. Without his encouragement and backing, this goal would not have been attained. I especially want to thank the cardiac anesthesiologists for their help and support during the study phase of my doctoral work. They were extremely helpful in guiding me during the study’s design and implementation. I want to also acknowledge Jerry Blum, CRNA for his superb intraoperative anesthetic maintenance of the patients during the study’s data collection. The most influential person at UCD was my mentor and friend, Dr. Neal Fleming. His long hours spent reading my IRB proposals, assisting me with my data collection and analysis, and reading (and re-reading) my dissertation is deeply appreciated. Observing his commitment to the education and the selfless hours spent with those who sought his help is inspiring and a role model I hope to emulate. It is through his dedication and guidance that I was able to complete this work.

My early days as a doctoral student at UCSF exposed me to a new world of knowledge that was invigorating after twenty years of practicing as a CRNA at the University of California

Davis Medical Center. I met new colleagues that would become my “community of scholars” and attended classes taught by some of the most gifted and experienced faculty in the nursing field. This is where I met two influential professors that became part of my dissertation committee: Drs. Kathleen Puntillo and Barbara Drew. I especially want to thank Kathleen for her continued guidance and support as I navigated through my class work, qualifying exams, and dissertation process.

Finally, and most importantly, I want to thank my family for their love and constant support throughout my doctoral education. To my wife, Sarah, for her understanding and patience when I stressed and vented to her with every new quarter’s assignments (especially Biostatistics). This is especially true for the last several months when I have been analyzing my data and writing my dissertation. To my daughters, Alison and Jenna, and my son-in-law, David, for their hours of listening and countless pep talks when I was threatening to quit. I truly apologize for any stress I brought on you all; you will never know how your words of encouragement made the difference between quitting and heading back into the classroom. I am sincerely blessed to have a family that encourages fulfilling one’s dreams. I hope that my goal to return to school and obtain my PhD will stand as an example that you are never too old to learn; words that were given me by my parents nearly a half century ago. I am hopeful that my new granddaughter, Ella, will someday pursue her educational goals and know how important it is to follow your educational dreams.

Abstract

The Use of Transesophageal Echocardiography for the Assessment of Left Ventricular Volume and Function in Patients Undergoing Acute Normovolemic Hemodilution as a Human Hemorrhagic Model

BACKGROUND: Since the development of the sphygmomanometer in 1896, the several methods to monitor volume resuscitation in hypovolemic trauma patients have been examined. Recently, transesophageal echocardiography (TEE) has been considered for this use. **PURPOSE:** This study examined the use of TEE for the assessment of left ventricular volume and function during graded blood removal in a human hemorrhagic model. **DESIGN:** Following IRB approval, 38 patients undergoing acute normovolemic hemodilution (ANH) intraoperatively were consented to have 15% of their total blood volume removed (according to ANH protocol) in 5% aliquots and stored in the operating room for re-infusion. After blood withdrawal, 5% aliquots of Hextend[®] was infused, equal the amount of blood removed. Left ventricular (LV) chamber dimensions and trans-mitral Doppler flow measurements were obtained with TEE at baseline and at each blood withdrawal and replacement of Hextend[®]. LV measurements analysis included: one-dimensional (1D) end-diastolic diameter (EDD), end-systolic diameter (ESD), and fractional shortening (FS); two-dimensional (2D) end-diastolic area (EDA), end-systolic area (ESA), and fractional area change (FAC); three-dimensional (3D) end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF); trans-mitral Doppler flow measurements of E and A-wave morphology. **RESULTS:** Statistically significant differences were demonstrated for measurements of: 1D EDD ($p < .0001$) and ESD ($p < .0001$); 2D EDA ($p < .0001$) and ESA ($p < .0001$) during blood removal. No statistically significant differences were

observed for FS ($p = .371$) or FAC ($p = .369$). Statistically significant differences were demonstrated for 3D measurements of EDV ($p < .0001$) and EF ($p = .002$) during both blood removal and replacement with Hextend[®]. No statistical significance was observed with ESV measurements ($p = .427$). Only the trans-mitral Doppler measurement of peak E-wave velocity demonstrated a statistically significant difference ($p < .0001$). CONCLUSION: Although all measurements of LV dimensions can detect 5% changes during blood removal, 3D measurements of EDV and EF can detect changes during both blood removal and replacement of Hextend[®], possibly making it better at guiding volume replacement during blood loss. Trans-mitral Doppler flow may not be as effective as a guide for fluid management.

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An Overview of Hypovolemic Shock, the Evolution of Trauma Care in the US, and Methods of Measuring Intravascular Volume and Cardiac Preload in the Management of Hypovolemia

Introduction

Hypovolemic shock, also known as hemorrhagic or traumatic shock, is associated with traumatic injury where intravascular volume is lost resulting in hemodynamic instability. The pathophysiology of hypovolemic shock is complex and involves a cascade of physiological events that include virtually every organ system in the body. The systemic microcirculation adjusts in a hierarchical fashion to preserve cardiac output and perfusion to the heart and brain.

The phenomenon of hypovolemic shock has been studied and attempts have been made to optimize prehospital and Emergency Department resuscitation and care of the severely traumatized hypovolemic patient. Early evaluation and initiation of care in the prehospital setting combined with aggressive resuscitation in the Emergency Department (ED), Operating Room (OR), and Intensive Care Unit (ICU) have improved patient outcomes (Dutton, 1999; Maier, 2003; Moore, McKinley, & Moore, 2004; West, Trunkey, & Lim, 1979).

Initial and continued evaluation of the trauma patient includes monitoring devices that can provide an accurate measurement of the intravascular volume status. Hemodynamic instability must be quickly and correctly identified and on-going accurate measurements are necessary to reliably guide resuscitative efforts. Clinical monitoring equipment is utilized to evaluate the trauma patient, from simple noninvasive blood

pressure and pulse measurements to more invasive techniques that include the monitoring of central venous and pulmonary artery pressures.

This chapter will review the phenomena surrounding hypovolemic shock as a result of trauma and provide an overview of the current practice of “trauma care.” In addition, an overview of various methods for measuring and estimating the intravascular volume will be presented. A newer technique, transesophageal echocardiography, will be presented as an addition to the more traditional approaches of intravascular volume assessment and management. Following this comprehensive review, the need for further investigation of transesophageal echocardiography as a method of perioperative fluid management will be presented as the basis of this study.

The Phenomenon of Hypovolemic Shock as a Result of Trauma

The term “shock” was first used in 1815 in a paper entitled: *On Gunshot Wounds of the Extremities* by the English surgeon Guthrie to describe the pathophysiology resulting from injury (Dutton, 1999). Fifty-seven years later, in 1872, Gross described shock as “a rude unhinging of the machinery of life” (Dutton, 1999; Gross, 1872). Theories as to the underpinnings of shock that were debated during this time included the release of systemic toxins from injured muscles, vagal hyperactivity resulting in vasomotor atony, and cardiac exhaustion. It was not until the early 1900s that hypovolemia was established as the principal cause of shock associated with traumatic injury (Dutton, 1999).

Hypovolemic shock is the most common form of shock in the trauma patient population and occurs as a result of a deficit in intravascular volume (Stene, J. K., Grande, C. M., Giesecke, A, 1991). This blood loss, if large enough, can affect oxygen

delivery to the microcirculation of various organs. Typically, blood loss is expressed in percentages of total estimated blood volume and categorized into four classes by the Committee on Trauma of the American College of Surgeons (Table 1.1).

	CLASS I	CLASS II	CLASS III	CLASS IV
Blood loss (mL)	Up to 750	750–1500	1500–2000	>2000
Blood loss (% blood volume)	Up to 15%	15%–30%	30%–40%	>40%
Pulse rate	<100	>100	>120	>140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Respiratory rate	14–20	20–30	30–40	>35
Urine output (mL/hr)	>30	20–30	5–15	Negligible
CNS/Mental status	Slightly anxious	Mildly anxious	Anxious, confused	Confused, lethargic
Fluid replacement (3:1 rule)	Crystalloid	Crystalloid	Crystalloid and blood	Crystalloid and blood

Table 1.1. Estimation of hemorrhage based on the volume loss as a percentage of total blood volume and described in classes. From the Committee on Trauma, American College of Surgeons, 2004, with permission.

Class I hemorrhage is defined by a 15% blood loss, which is approximately 750ml if one assumes a 5,000 ml estimated total blood volume, and is associated with minimal physiologic alterations. Class II hemorrhage is defined as a 15% to 30% loss (approximately 1500 ml in a 5,000 ml blood volume) and results in autonomic physiological responses noted in Table 1.1. Class III and Class IV hemorrhages are defined by blood losses of 30% to 40% and >40%, respectively. These trauma patients are estimated to have lost at least 2,000 ml or more of blood and exhibit pathophysiologic evidence of significant intravascular volume deficit as shown in Table 1.1.

As the intravascular volume is depleted, a constellation of changes occurs in virtually every physiologic system in the body. This cascade of physiological events is

initiated by the body's early warning system to hypovolemia, namely the pressure sensitive baroreceptors in the aortic arch and carotid sinuses, the autonomic cardiovascular control centers in the medulla of the central nervous system, and the pressure sensitive vasculature of the renal system. Although an in-depth review of the pathophysiology of hypovolemic shock is beyond the scope of this paper, a diagrammatic overview of this phenomenon is presented in Figure 1.1 (Boulpaep, 2003b).

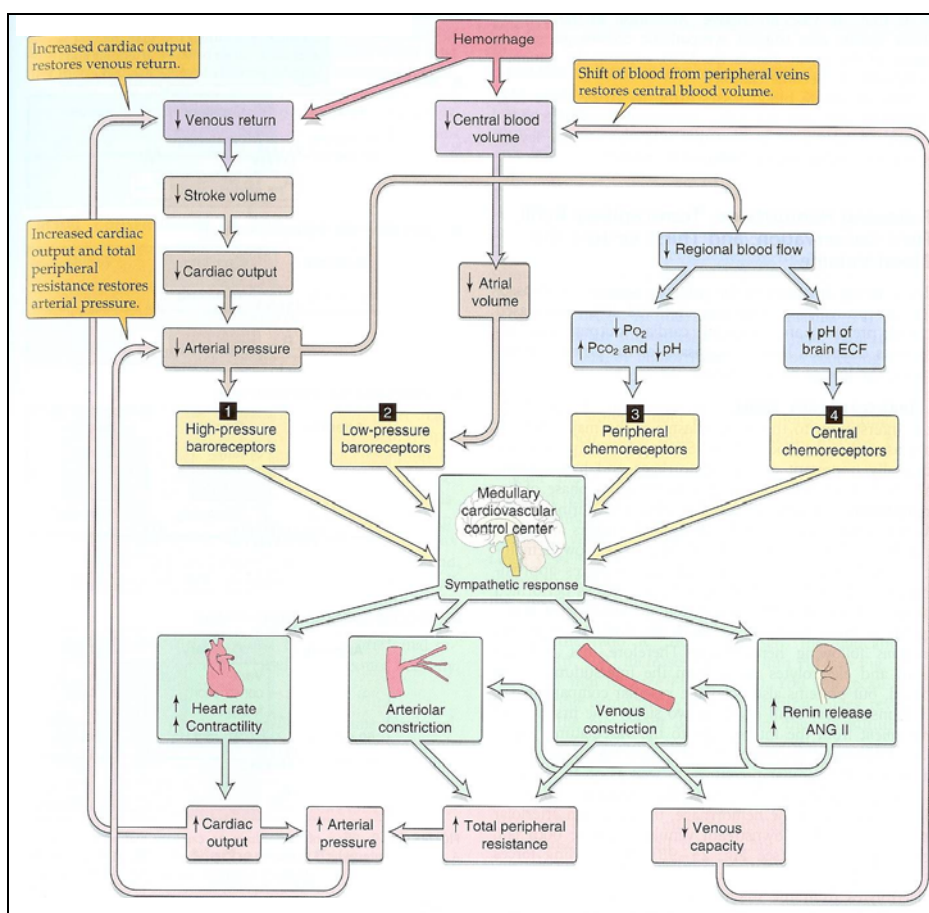


Figure 1.1. Pathophysiological changes associated with hypovolemia. Blood loss (hypovolemia) initiates a cascade of physiological responses based on four receptor activations. From Boulpaep, E.L., *Integrated Control of the Cardiovascular System*, In: Boron, W.F., Boulpaep, E.L., *Medical Physiology*, 2003, p. 587, with permission.

At the cellular level, the physiological response to hemorrhage and hypovolemic shock is determined by the degree of hemorrhage (i.e.: Class I, II, III, IV), the amount of oxygen delivered to the cells during the hypotensive episode, the length of time before

volume is restored, the age, and the underlying pre-morbid condition of the patient (Boulpaep, 2003b; Dutton, 1999; Hannan, 2004; Stene, J. K., Grande, C. M., Giesecke, A, 1991). All of these variables impact upon the cellular response to the hypoxic/anoxic event induced by decreased oxygen delivery as a result of hypovolemia. The magnitude of the insult will determine if the cellular injury is sub-lethal and, therefore, reversible or lethal leading to cell necrosis and death.

The hallmark of hypovolemic shock is decreased oxygen delivery, which results in cellular hypoxia. The mitochondria reduce the amount of adenosine triphosphate (ATP) produced in the presence of hypoxia, which causes a decrease in the Na-K-ATPase activity. Intracellular sodium concentration rises with a concomitant decrease in intracellular potassium concentration, which causes an increase in the cell's resting membrane potential from -90mv to -60mv . Water from the interstitial compartment enters the intracellular compartment causing cellular edema (J. K. Stene, Grande, C. M., Giesecke, A, 1991).

If this scenario is allowed to continue without intervention, cellular deterioration continues until irreversible shock and inevitable death occurs. These deteriorating changes take place at different rates in different organ systems. For example, the kidney develops irreversible hypoxic/anoxic changes faster than the bronchial epithelium (Stene, J. K., Grande, C. M., Giesecke, A, 1991). This is a result of the decrease in splanchnic and renal perfusion associated with the autonomic physiological changes induced by hypovolemic shock. In an attempt to survive, the body initiates a hierarchical approach to systemic organ perfusion that preserves cardiac output to the heart and brain at the expense of other organ systems. The final common pathway to death from hypovolemic

shock is the cumulative effect of a critical number of cells in various organ systems reaching an irreversible anoxic state (Dutton, 1999; Stene, J. K., Grande, C. M., Giesecke, A, 1991).

Early diagnosis and aggressive treatment of severe hypovolemic shock is paramount in optimizing the likelihood for survivability after significant injury (Class III and IV hemorrhage). Military wartime experience of early intravascular volume replacement in the field (prehospital), combined with prompt evacuation for definitive hospital care of the injured combatants, helped to establish the concept of trauma care in the United States (Rose, 1998). The early assessment and aggressive treatment of hypovolemic shock is now considered to be the standard in trauma resuscitation in many countries of the world (Gupta, 1999).

The Establishment of Trauma Care in the United States

In the United States, trauma ranks as the third most common cause of death and is the leading cause of death for individuals under the age of 44 (Dutton, 1999; Gupta, 1999; Maier, 2003). According to the National Safety Council, unintentional injuries in 2002 totaled 24.6 million. This translated to a total cost of \$586.3 billion dollars in medical costs as well as in productivity and wages lost (Council, 2003). More specifically, trauma results in approximately 150,000 deaths per year with severe hypovolemia from hemorrhage as the major factor in nearly half of those deaths (Maier, 2003; Stene, J. K., Grande, C. M., 1991).

The National Trauma Data Bank™, which has collected trauma-related injuries and death since 1989 for the American College of Surgeons

(www.facs.org/trauma/ntdb.html), identified specific age groups that have the highest incidence of injuries from unintentional trauma (Figure 1.2) (Fildes, 2003).

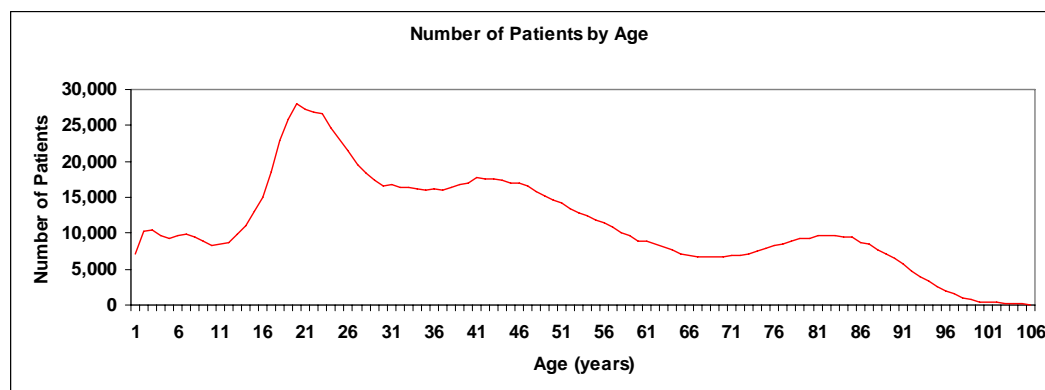


Figure 1.2. Number of injured patients reported by age. National Trauma Data Bank, American College of Surgeons, 2006, with permission.

Three peaks are noted in Figure 1.2. The first occurs between 17 and 24 years where motor vehicle collisions and gunshot wounds are the leading causes of injuries. The second peak is at 35-44 years where motor vehicle collisions are the leading cause of trauma. The third peak occurs at 72-85 years of age where motor vehicle collisions and falls account for the majority of injuries. Figure 1.3 identifies the injury age groups by gender, which reveals that females make up the largest number of injuries in the 72-85 year age group. This increase in female injuries may be due to women having a higher incidence of falls (Gupta, 1999).

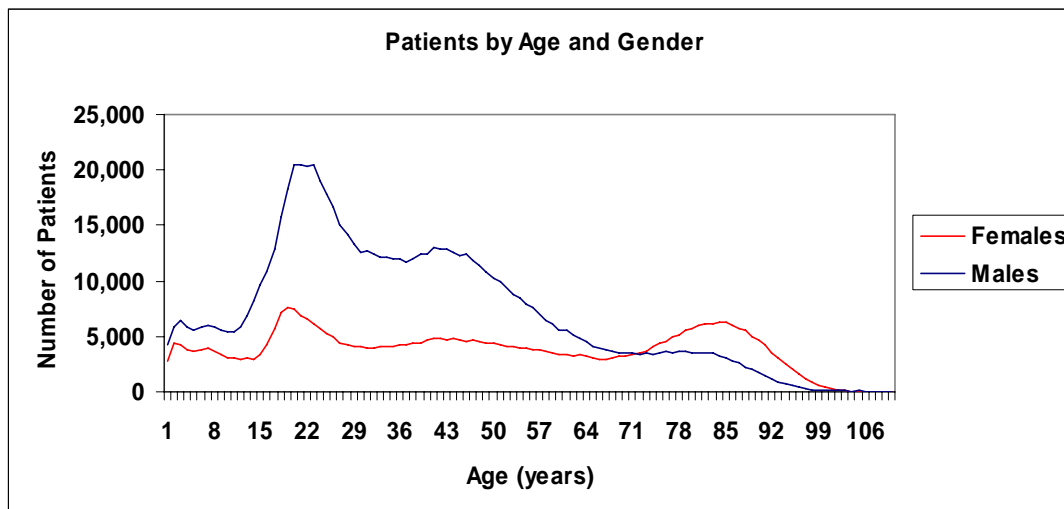


Figure 1.3. Number of injuries reported by age and gender. National Trauma Data Bank, American College of Surgeons, 2006, with permission.

Figure 1.4 relates the number of patients by age and mechanism of injury.

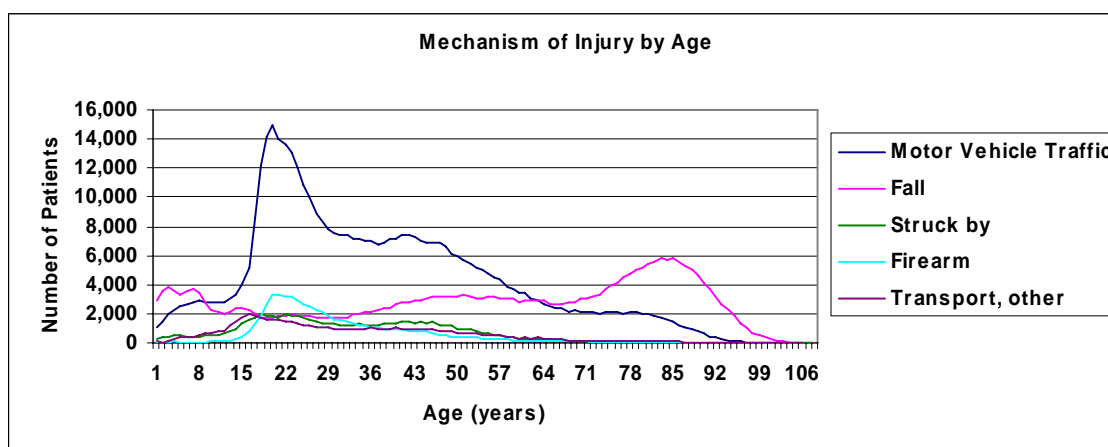


Figure 1.4. Mechanism of injury reported by age. National Trauma Data Bank, American College of Surgeons, 2006, with permission.

This figure illustrates the significant increase in motor vehicle collisions that occur in the late teens and early twenties. Injuries associated with violence begin to rise in the mid to late teens with a sharp decrease in the early to mid forties. Falls account for the majority of injuries in the seventy and eighty year old population.

The development of “trauma centers” to care for injured victims has significantly reduced the death rate by early and effective prehospital and hospital treatment (Maier, 2003). Their beginnings took root in the 1960s during the Vietnam War, where major

advances in the care of severely injured soldiers were facilitated by well-organized prehospital care and early definitive treatment (Rose, 1998). The first trauma center in the U.S. was developed by Dr. R. Adams Cowley in Baltimore at the Maryland Shock Trauma Institute, which is affiliated with the University of Maryland (Stene, J. K., Grande, C. M., 1991). Later, the ground-breaking work by West and colleagues in San Francisco demonstrated a reduced death rate from >30% in Orange County, where there were no trauma centers, to <5% in San Francisco where injured patients were transported to a dedicated trauma center (West et al., 1979). The potentially unpreventable mortality rate for patients admitted to trauma centers is now considered to be between 1% and 3% (Maier, 2003).

Three levels of trauma centers have been developed and adhere to standards published by the American College of Surgeons (Figure 1.5) (Stene, J. K., Grande, C. M., 1991).

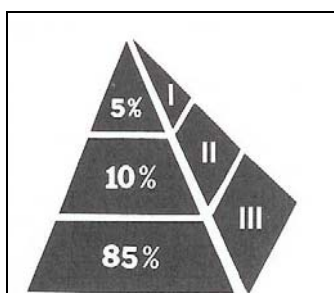


Figure 1.5. Distribution of trauma cases to Level I, II, and III trauma centers. From Stene, JK and Grande, CM: Trauma Care, p. 5, with permission.

Most trauma patients (85%) can be managed by local emergency rooms or Level III trauma centers that provide trauma-experienced staff 24 hours per day. Severely injured patients that are brought to these hospitals and are found to require more specialized care (eg. neurosurgical) are stabilized and transported to a higher echelon of care. Level II trauma centers are available for those patients requiring immediate general or

neurosurgical intervention (15%). These centers must also have a lighted heliport and must care for 300-600 trauma cases per year. Level I trauma centers care for the most severely injured patients (5%). Level I trauma centers provide immediate care in all surgical specialties, have dedicated resuscitation rooms in their Emergency Department, and have a prepared trauma operating room staffed 24 hours a day. They are usually affiliated with academic teaching programs and research centers that also provide public education regarding trauma. These centers must care for 600-1000 trauma patients per year to maintain Level I accreditation from the American College of Surgeons.

In addition to early and definitive treatment of trauma patients, a classic survey by Trunkey established the trimodal distribution pattern of death due to injury that is illustrated in Figure 1.6 (Trunkey, 1983).

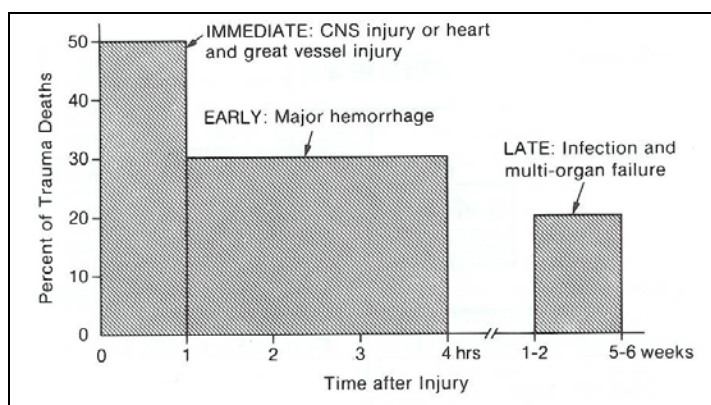


Figure 1.6. The trimodal distribution pattern of death as a result of trauma. From Brown, DL. Trauma management: the anesthesiologist's role. *Int. Anesthesiol Clin* 1987;25:1-18, with permission.

“Immediate” death, which occurs in 50% of the victims within the first hour, is a result of massive injuries to the central nervous system or the heart and the great vessels.

“Early” death from major hemorrhage occurs between one and four hours post-trauma and accounts for 30% of the deaths. “Late” death occurs between one and six weeks after the injury and is associated with infection and/or multisystem organ failure. This crucial early work facilitated the development of the present day trauma system to identify the

5% to 12% of the patients with significant injuries that have the best odds of survival when transported to and treated at a Level I and II trauma centers (Caplan, 1997; Stene, J. K., Grande, C. M., 1991).

Over the last decade, trauma care has resulted in an optimizing of prehospital care of severely injured patients with prompt intravascular access and volume replacement. This, combined with aggressive resuscitative efforts in the Emergency Department and rapid “damage control” surgical intervention has led some to believe that the original trimodal pattern of death described by Trunkey may need to be re-examined (Dutton, 1999; Maier, 2003; Stene, J. K., Grande, C. M., 1991). This is especially true given the proportionally large group of critically injured patients that is now being admitted to the ICU or taken to the operating room for emergency surgery (Figure 1.7 and Table 1.2).

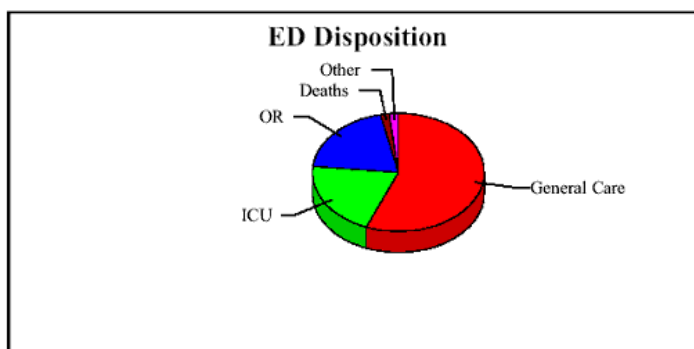


Figure 1.7. Disposition of trauma patients from the Emergency Department. A large proportion is transferred to the Intensive Care Unit and the Operating Room. From National Trauma Data Bank, 2003 (N = 488,553), with permission.

Disposition	Percent of Total	Number of Patients
General Care	56%	273,596
ICU	20.75%	101,384
OR	19.94%	97,421
Deaths	1.73%	8,437
Other	1.58%	7,715
Total	100%	488,553

Table 1.2. Identifies the numbers of patients and the percentages associated with the ED dispositions shown in Figure 7. From National Trauma Data Bank, 2003.

The immediate evaluation of the unconscious hemodynamically unstable trauma patient in Level I and II trauma centers is now accomplished with the aid of a hand-held ultrasound device that can identify fluid in the abdominal and/or chest cavities. This technique, called Focused Abdominal Sonography for Trauma (FAST), is one example of how noninvasive ultrasound technology is providing instantaneous information concerning the differential diagnosis of hemodynamic instability, especially in the unconscious and pediatric trauma population (Biffl, Moore, & Kendall, 2000; Chelly et al., 2004; Coley et al., 2000; Shackford, 1998).

A Critical Analysis of Methods to Assess Intravascular Volume in Hypovolemic Trauma Patients

The optimal evaluation of the hypovolemic patient requires an accurate assessment of intravascular volume. Since the development of the sphygmomanometer by Scipione Riva-Ricci in 1896, practitioners and researcher have examined methods of assessing intravascular volume status. The traditional use of blood pressure and pulse measurements continue to be the mainstay of initial volume assessment in the trauma patient. These indices, however, often provide an imprecise numerical guide of a patient's intravascular volume, especially in the hypovolemic trauma patient population. Because of the previously described sympathetic activation via the autonomic nervous system's response to hypovolemia, an accurate assessment of intravascular fluid volume is not possible using indirect measurements such as low blood pressure, decreasing pulse pressure, and rapid pulse to assess the degree of hypovolemia.

Later in the resuscitative process, more invasive monitoring techniques such as central venous and pulmonary artery pressure measurement may be employed in an attempt to evaluate intravascular volume and guide on-going fluid/colloid replacement. In

a review of shock resuscitation, Moore and colleagues advance the notion that a noninvasive monitor is still needed that can provide rapid assessment of intravascular volume (Moore, 2004).

The introduction of routine intra-arterial invasive monitoring enabled a continuing assessment of the blood pressure (Lake, 1990a). However, the arterial vascular bed is considered to be a “high resistance” system and is under constant pressure. This high-pressure system accounts for approximately 20% of the total blood volume (Mohrman, 2003). The high resistance arterial system is responsible for providing the force that delivers oxygenated blood to the capillary beds for nutrient exchange at the cellular level. This high resistance vascular bed, however, does not adequately reflect the overall capacitance of the intravascular system.

The ability to measure central venous pressure (CVP) further advanced the assessment of patient’s exhibiting hypovolemia (Lake, 1990b). A catheter placed at the junction of the inferior and superior vena cava provides an indication of the pressure within the venous capacitance vessels, which account for approximately 65% of the total blood volume (Mohrman, 2003). In a normally functioning heart, CVP is helpful in determining venous return by following pressure trends during volume resuscitation. Knowledge of the central venous pressure and therefore right heart pressures does not, however, provide critical information regarding left heart pressure and function.

A more direct assessment of left ventricular pressure occurred with the development of the pulmonary artery catheter (PAC) (Lake, 1990b). The PAC is introduced in a similar fashion to the CVP catheter and then is passed into the right atrium, right ventricle, and pulmonary artery via a flow-directional balloon attached near

the catheter tip. The catheter, with the balloon inflated, is allowed to “wedge” itself against a small branch of the pulmonary arterial circuit. With the balloon inflated, the distal catheter lumen senses only the pressures being generated by the left atrium. In the absence of mitral valve disease and pulmonary vascular disease, this pressure is thought to be a reflection of the left ventricular end-diastolic pressure. Intracardiac pressure, however, can be an inaccurate measurement of true cardiac filling (cardiac preload), especially in the trauma patient population because of the significant cardiovascular and pathophysiologic changes associated with shock previously described and illustrated in Figure 1.1 (Boulaep, 2003b; Dutton, 1999; Stene, J. K., Grande, C. M., Giesecke, A, 1991). Finally, knowing the cardiac volume (preload) does not provide information on whether the heart is delivering the blood to the cells effectively. Therefore, a monitor that evaluates both cardiac volume and function is needed; without this capability, a therapeutic end-point for volume resuscitation will be difficult to attain.

To this end, transesophageal echocardiography (TEE) has recently been utilized for rapid, real-time cardiac assessment (Maslow, 2003a; Otto, 2000; Troianos, 2002). TEE provides a direct “window” into the heart, which facilitates prompt evaluation of both cardiac function and left ventricular volume status. This relatively non-invasive procedure can accurately assess whether the hypotension observed in a trauma patient is due to a mechanical dysfunction (e.g. aortic or cardiac injury) or hypovolemia. In the fast paced tempo of trauma care, TEE can quickly provide a reliable measurement of a patient’s volume status and cardiac function (Cahalan, 2004).

Historical Overview of Transesophageal Echocardiography

Although ultrasound echo technology has been known and used in medical diagnosis for many years, its use to evaluate cardiac function is relatively new. The technology of echocardiography dates back to the first M-mode echocardiograph in 1976 (Frazin, 1976). It was later described for the monitoring of continuous left ventricular function during cardiac surgery (Matsumoto, 1980). The first two-dimensional phased array transducer was mounted on the tip of a flexible gastroscope at the University of Hamburg in 1982 (Schluter, 1982). Echocardiography has two approaches for the examination of cardiac structures. Finally, in the mid-1980s, the doubling of the piezoelectric crystals (discussed in Chapter 2) in the transducer probe made the echocardiograph images powerful enough for TEE to be utilized for intraoperative cardiovascular assessment.

Transthoracic Echocardiography (TTE), the lesser invasive of the two techniques, approaches cardiac interrogation by placing the transducer on the exterior chest wall to obtain the cardiac images (Otto, 2000). Limitations of TTE are that it cannot acquire images of posterior cardiac structures such as the pulmonary vein, left atrium, and mitral valve and is interfered by the respiratory cycle. In addition, intervening lung and bone tissue compromises image quality. TEE reduces the limitations encountered with TTE by placing the probe in the esophagus and closer to the cardiac structures permitting the use of a higher frequency probe for enhanced image resolution. The limitations to TEE in the non-trauma population are the common requirement for conscious sedation in the awake patient and the insertion of the probe into the esophagus (Otto, 2000; Troianos, 2002). This is thought to be a minimally invasive procedure considering other measurement

techniques such as the PAC and CVP placement. Sedation is not usually given to a trauma patient because of its hemodynamic effects of lowering the blood pressure in an unstable patient and the possibility of vomiting and aspiration in a patient who has a full stomach.

Cardiac volumes and structural function have been assessed and documented with the TEE for twenty years. Cardiac anesthesiologists were the first to utilize intraoperative TEE in the mid-1980s primarily on cardiac surgical patients (Cahalan, Litt, Botvinick, & Schiller, 1987). TEE has been found to be a valuable tool to evaluate the function and surgical repair of cardiac structures such as mitral and aortic valves (Lake, 1990c; Maslow, 2003a; Otto, 2000; Troianos, 2002). TEE was also discovered to be a sensitive indicator for evaluating regional ventricular wall motion (Huemer, Kolev, & Zimpfer, 1994; Loubieres et al., 2000; Skiles, 2000). Other work has investigated the associations between cardiac chamber size, preload, volume status, and cardiac output in critically ill patients in the ICU (Hanowell, 1998; Konstadt, Thys, Mindich, Kaplan, & Goldman, 1986; Lake, 1990c; Otto, 2000; Tousignant, 2000; Troianos, 2002; Wolrab, Weber, Tschernich, Andel, & Huemer, 1997).

Potential Approach of Quantifying Hemorrhage with the TEE

An effective measurement of intraoperative volume replacement in large volume blood loss has always been of keen interest to this author. For decades volume replacement in the severely injured trauma patient was guided by either blood pressure and pulse or CVP measurements. CVP and especially PAC placement are difficult to place because of the valuable time consumed in the insertion of these catheters. In addition, the surgical trauma skin prep requires that a sterile area include from the entire

neck (at the border of the mandible) to the knees and laterally to the OR table.

Frequently, this prevents the placement of intravascular monitoring devices like the CVP and PA catheters in the operating room, requiring their insertion when the patient arrives in the ICU. This results in the volume resuscitation being guided by arterial blood pressure, which is not an accurate reflection of intravascular capacity. In addition, TTE is not a viable option because of the surgical skin prep described above and the possibility that the chest may be open for the surgical procedure.

Recent studies have expanded the use of TEE from the cardiac specialty to its utility in monitoring of patients undergoing non-cardiac surgical procedures (Hanowell, 1998). Measuring left ventricular chamber dimensions and utilizing Doppler flow to calculate cardiac output are now an integral part of quantitative hemodynamic volume analysis with the TEE (Otto, 2000). Another unique advantage of TEE is its capacity to evaluate cardiac structural function and integrity. The important feature of concurrently assessing both volume and function can be invaluable when determining if hypotension is due to hypovolemia or cardiac injury (Cahalan, 2004). TEE has also been described for the rapid assessment of the thoracic aorta to rule out injury (Aaluri et al., 2000).

The ability of the TEE to quantify a known volume of on-going blood loss in a human hemorrhagic model has not been thoroughly investigated. To identify if TEE would be useful in the assessment of intravascular volume by determining left ventricular preload in the hypotensive trauma patient, research must first be directed toward a stable human hemorrhagic model. Elective surgical patients undergoing acute normovolemic hemodilution (ANH) as part of their intraoperative anesthetic plan provide an ideal human model to investigate this method of volume assessment. Under these stable

conditions, TEE can be evaluated for its accuracy and reliability for assessing on-going blood loss.

Overview of Acute Normovolemic Hemodilution

Acute normovolemic hemodilution (ANH) is used in selected surgical procedures to decrease a patient's red cell mass prior to intraoperative blood loss (Jobes & Gallagher, 1982; Monk & Goodnough, 1998; Rottman & Ness, 1998; Stehling & Zauder, 1991). The procedure calls for the removal of red blood cells from the patient and the infusion of either crystalloid (normal saline or lactated ringer's) or colloid (albumin or Hextend[®]) solution to re-establish the intravascular volume. The concept is that the patient will lose dilute blood during the surgical procedure and then be re-infused with his/her own blood after the major blood loss is complete. In addition to the red blood cells, the patient also receives their plasma, which has both volume expansion properties and clotting factors.

The process for collecting and storing the shed blood follows an established hospital protocol. The blood removal is initiated after general anesthesia is induced and a large-bore IV or central venous access is established. The amount of blood removed is based on the patient's calculated estimated blood volume: men = 70ml/Kg and women = 65ml/Kg. The shed blood is collected in sterile blood collecting bags that contain 50ml of citrate-phosphate-dextrose (CPD) to prevent clotting while it is stored in the OR at room temperature. The total amount of blood removed averages 1000ml or 15% to 20% of the patient's blood volume, representing a class II hemorrhage shown in Table 1.1. Common procedures in which intraoperative ANH is used are major vascular (aortic) (Cina & Bruin, 1999), orthopedic (scoliosis) (Bak, Abildgard, Lisander, & Janerot-Sjoberg, 2000), urological (prostate) (Terada et al., 2001), and gynecologic (hysterectomy) (Rehm et al.,

2000). It has even been used for patients undergoing multiple aesthetic plastic procedures (Almeida, 1999).

TEE has been used to investigate if ANH is safe in patients with diagnosed coronary artery disease (CAD). Early work by Catoire and colleagues in France found that ANH did not worsen left ventricular wall motion, which is an indication of ischemia, in patients diagnosed with CAD who were undergoing aortic valve surgery (Catoire, 1992). Left ventricular wall motion and trans-mitral Doppler flow by TEE was also studied by Bak and associates in Sweden on patients undergoing ANH for scoliosis surgery and it was not found to compromise systolic or diastolic function (Bak et al., 2000). Similar findings were reported by Licker and colleagues from Switzerland where TEE Doppler detected an improved venous return, increased preload, and increased cardiac output with ANH in patients with CAD undergoing CABG (Licker, Sierra, Tassaux, & Diaper, 2004). Finally, Vara-Thorbeck and Gurerro-Fernandez Marcote reported the safety of ANH in patients over 60 years of age undergoing abdominal and major orthopedic surgery (Vara-Thorbeck & Guerrero-Fernandez Marcote, 1985). These investigators reported no adverse effects in elderly men and women with any history of cardiac disease when the hematocrit was lowered to 27% to 29%.

The safe and established practice of acute normovolemic hemodilution provides an excellent opportunity to assess if TEE is accurate and reliable in quantifying a known volume of controlled blood loss. TEE is an effective tool in the rapid assessment of hypotension in the critical care and trauma patient population with respect to volume and cardiac function (Andel et al., 1997; Brown, 2002; Cahalan, 2004; Oh et al., 1990; Otto, 2000). Studies that use TEE to evaluate volume status are performed manually on-line

and off-line or beat to beat with an on-line technique called automated border detection (ABD) or acoustic quantification (AQ). (Cahalan, 2004, 1993; Cheung, Savino, Weiss, Aukburg, & Berlin, 1994; Gorcsan et al., 1994; Hanowell, 1998; Lake, 1990c; Otto, 2000; Reich, Konstadt, Nejat, Abrams, & Bucek, 1993; Swenson, Harkin, Pace, Astle, & Bailey, 1996; Troianos, 2002). An in-depth discussion of these techniques will be presented in the following chapter.

The Need for Further Study

Trauma care has evolved over the last five decades and continues to focus on early identification and aggressive treatment of severe hypovolemia from hemorrhage. The ability to promptly identify those patients who are hemodynamically unstable from hypovolemia and effectively guide their resuscitative efforts with TEE may contribute to the overall survivability of trauma patients. Rapidly establishing oxygen delivery to the microvasculature through efficient intravascular volume replacement may decrease the number of patients who die from hemorrhage in the first few hours after their injury and multiple organ failure in the days that follow their trauma. Innovative noninvasive ultrasound technology continues to enhance assessment of the trauma patient. Transesophageal echocardiography is a relatively new technique for the monitoring of the trauma and critical care patient population. However, the utilization of transesophageal echocardiography to assess intravascular volume replacement in the high tempo resuscitative environment of the operating room has been neither investigated nor established. In order to advance its use in this resuscitative environment, TEE must first be evaluated in a more controlled setting. Intraoperative acute normovolemic

hemodilution provides an ideal clinical condition to determine the capability for TEE to quantify a known volume of controlled hemorrhage.

Purpose of the Study

In clinical practice, it is important to have a monitor that can be quickly placed, is relatively safe and non-invasive. In addition, this monitor should provide a prompt, reliable assessment of on going blood loss and volume replacement. Transesophageal echocardiography meets these needs with a probe that can be quickly placed and is relatively safe and non-invasive. The purpose of this study is to determine if TEE can reliably measure a calculated volume of blood removal and replacement with colloid in a controlled human hemorrhagic model with patients undergoing intraoperative acute normovolemic hemodilution. This study will evaluate the effects of graded blood loss and replacement with colloid on left ventricular preload as measured by two-dimensional and three-dimensional volume assessment and diastolic function as measured by trans-mitral Doppler flow velocity.

TRANSESOPHAGEAL ECHOCARDIOGRAPY: From the physical properties of sound waves to the evolution of transesophageal echocardiography as a method for the assessment of left ventricular function and volume

Introduction

This chapter will review the use of transesophageal echocardiography in the perioperative and critical care patient population. A complete discussion of echocardiography, however, must first begin with an overview of the physical properties of sound waves and how ultrasound waves are used to create both two-dimensional and Doppler images. The purpose of this paper is to acquaint the reader with the basic physics that are intrinsic to echocardiography, introduce the technical attributes that have made echocardiography an integral part of perioperative and critical care patient assessment, and present a substantive literature review of its use in intraoperative volume assessment. Because of the technical terminology used, a Glossary of Terms is presented in Appendix 1.

Overview of the Physical Properties of Sound Waves

Sound waves are vibrations propagated within a physical medium, in this case, human tissue (Maslow, 2003a; Otto, 2000). As sound waves pass through different tissues, they interact with areas of compression (molecules that are tightly bound) and rarefaction (molecules that are loosely bound) producing a sine wave. Humans hear sound waves with a frequency between 20 Hertz and 20 kilohertz (kHz). Frequencies above this range are called ultrasound waves. Diagnostic medical ultrasound devices use frequencies of between 1 million and 20 million Hertz or 1-20 megahertz (MHz).

Sound waves are measured by their physical characteristics (Maslow, 2003a). Amplitude is the height of the sound wave perpendicular to the wavelength. Frequency is the number of sine wave cycles per second and is measured in Hertz. Wavelength is the length of one cycle and is measured in millimeters. These sound wave measurements determine the velocity of the vibrations through the tissue medium:

$$\text{velocity} = \text{wavelength} \times \text{frequency} (v = \lambda \times f).$$

Sound waves interact differently with various types of tissues in the body as they pass through them. These interactions cause changes to the ultrasound signal as they pass through the body's tissues. Reflection of the ultrasound waves refers to their direct return to the transmitting source. Refraction occurs when the ultrasound waves bend, causing a change in their original direction. An important property of a tissue is its capacity for transmitting sound waves known as acoustic impedance. Attenuation refers to the loss or decrease in a sound wave's intensity as it travels through uniform tissue. There is an inverse relationship between the wavelength (λ) and frequency (f):

$$\lambda = v \times 1/f$$

This inverse relationship has consequences when comparing the depth of the penetration of the wave into tissue and the resolution of the objects visualized by the reflected sound waves (Maslow, 2003a; Otto, 2000). Higher frequency sound waves with shorter wavelengths result in better resolution of an image but at a loss of wave penetration into tissues. Lower frequency sound waves with longer wavelengths have deeper tissue penetration, however image resolution is decreased. The wavelength frequencies used in transesophageal echocardiography are between 3.5 and 7.5 MHz.

Formation of Ultrasound Waves in Echocardiography

Echocardiography technology uses the principle of piezoelectricity to create the ultrasound waves (Maslow, 2003a; Otto, 2000; Troianos, 2002). Piezoelectric crystals are made from quartz or titanite ceramic. When an alternating current is applied to the crystals, they compress and expand resulting in the generation of ultrasound waves. The nature and thickness of the piezoelectric crystals regulate the frequency of the ultrasound waves.

Piezoelectric crystals can both generate and receive reflected ultrasound waves. When ultrasound waves strike the piezoelectric crystal an electric current is generated. The crystal is therefore a “transmitter” and a “receiver” of ultrasound waves. The ultrasound pulse wave generated by a piezoelectric crystal is typically between one to six milliseconds, after which the crystal transducer switches to receiver mode and awaits the reflected ultrasound wave signal. This alternating of pulse wave transmission and receiving is sequentially repeated over time.

The transducer forms an image based on the time delay between the transmission and receiving of ultrasound waves. The time delay between the transmission and receiving of a signal is longer for structures that are deeper (farther from the transducer). The depth of the image is calculated based on the speed of sound in blood (1540 meters/second) and the time interval between the transmission and the return of the reflected signal. The signal received is then processed by computer software within the TEE machine that, depending on the type of internal software, results in the formation of a one-dimensional, two-dimensional, or three-dimensional image.

Ultrasound Imaging Modalities Used with Transesophageal Echocardiography

Over the past three decades, transesophageal echocardiography has evolved from its early developmental stage to an important monitor in assessing cardiac function.

Amplitude mode (A-mode) shown in Figure 2.1 below was the original display format (Frazin, 1976).

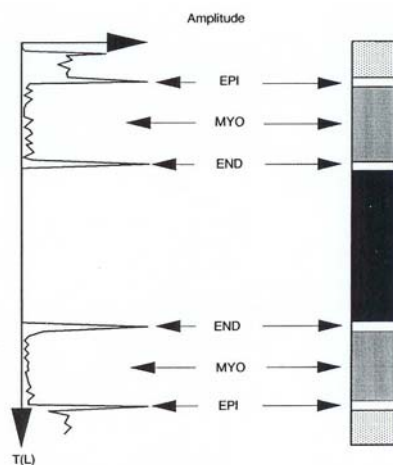


Figure 2.1. Amplitude mode (A-mode). EPI: Epicardium, MYO: Myocardium, END: Endocardium. From Oka and Goldiner, *Transesophageal Echocardiography*, 1992, p. 12, with permission.

Horizontal spikes along the vertical axis represented the amplitude of the returning signal wave. These spikes indicated both the distance and the strength of the returning echo waves. Present day imaging utilizes the brightness mode (B-mode) technology (Lake, 1990c). The B-mode converts the amplitudes of reflected echo waves into pixels of varying brightness along the vertical axis of the echocardiographic display. Brightness correlates with the strength of the returning wave signal and is shown in Figure 2.2

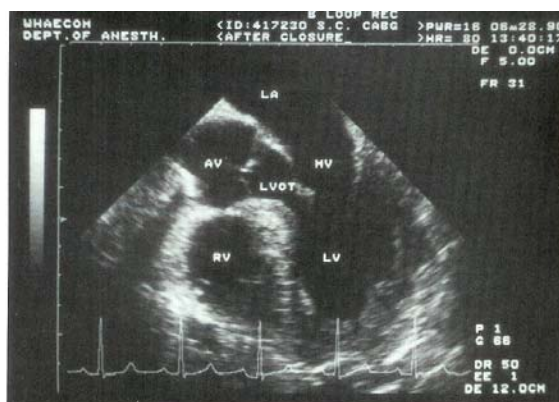


Figure 2.2. Brightness mode (B-mode). From Oka and Goldiner, *Transesophageal Echocardiography*, 1992, p. 10, with permission.

Motion mode (M-mode) provides a one-dimensional “ice-pick” view through the heart structures as is shown in Figure 2.3 (Otto, 2000; Troianos, 2002).

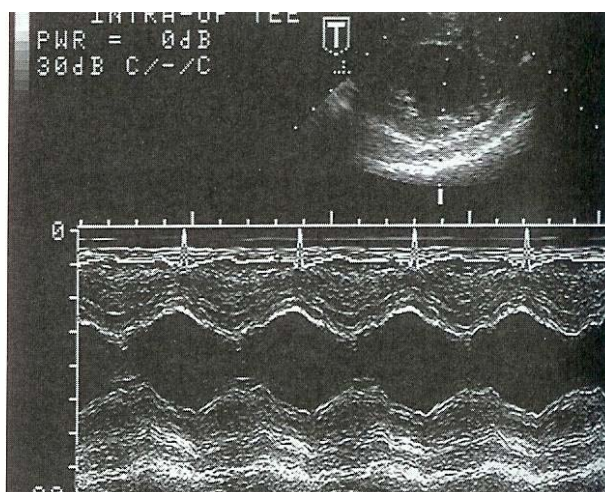


Figure 2.3. Motion mode (M-mode) of normal left ventricle. The TG SAX view at the top identifies the reference view from which the m-mode image is acquired. From Troianos CA, *Cardiac Anesthesia for the Cardiac Patient*, 2002, p. 130, with permission.

M-mode adds temporal information to the B-mode, with the time displayed on the vertical axis. The images are updated at a very high rate (1000 to 2000 frames per second), which provides a high quality axial image of the dynamic motion of the heart. M-mode is often utilized for examining the timing of cardiac events such as mitral and aortic valve motion when used in conjunction with the electrocardiogram. The m-mode’s

limitation is that it displays only axial motion and is unable to provide any lateral movement of cardiac structures.

Two-dimensional echocardiography modifies the B-mode and sequentially directs ultrasound waves across a section of the heart. Instead of directing a pulse in one direction (M-mode), the sequencing of the pulse waves provides both shape and lateral motion to the image obtained. Two-dimensional technology imaging is possible through the development of a transducer that consists of multiple crystals (piezoelectric) that are aligned next to one another; the term is called an “array” (Maslow, 2003a; Otto, 2000). The sound waves from each crystal combine to produce a uniform wave front that can be both directed and focused at a selected target of interest. Linear array imaging systems have a line of crystals enclosed in a long transducer housing that create an image located directly in front of the wave; this technology is commonly used in vascular and obstetrical practices. The phased array imaging system utilizes precise timing of the sequential crystal pulsation to control and focus the ultrasound waves producing an arc-shaped beam. This technology is most commonly used in transesophageal echocardiography because it allows for a smaller transducer size. Although two-dimensional echocardiography provides high-resolution images of cardiac structures in motion, its limitation is its inability to visualize blood flow.

Doppler Technology in the Evaluation of Cardiac Blood Flow and Volume Status

The Doppler effect occurs because the motion of an object causes sound waves to compress in the direction of the motion and expand in the direction opposite the motion (Maslow, 2003a; Otto, 2000). Red blood cells reflect ultrasound waves as they move through a blood vessel or cardiac structure. The velocity of blood flow is determined by using the Doppler effect to examine the change in ultrasound frequency of moving red

blood cells. By directing the ultrasound beam parallel to the flow of the red blood cells, Doppler echocardiography can assess the reflected waves to determine both the direction and speed of the blood flow. Blood flow towards the transducer compresses the reflected signal causing a higher frequency than the transmitted signal. Blood flow away from the transducer causes a lower frequency than that produced by the transducer's ultrasound wave. The term given to these changes in frequency is called "modulation." Evaluating the modulation in frequency with Doppler echocardiography results in a spectral display image. Spectral display refers to modulation data plotted as a velocity-time recording. Brighter pixels indicate frequencies with higher amplitude. The velocity-time display allows for real-time blood flow assessment, which is the basis for quantitative hemodynamic calculations. Various Doppler techniques are available for the evaluation of blood flow and are described in TEE textbooks (Lake, 1990c; Otto, 2000).

Pulsed wave Doppler uses a single crystal to both send (in bursts) and receive ultrasound waves. To make an accurate determination of the receiving wavelength, it must be sampled at least twice in each cycle. Because data are collected intermittently, the maximal frequency and blood flow velocity measurements are limited. Therefore, the maximal frequency (F) created by the velocity of the red blood cells must be half the pulse repetition frequency (PRF) of the interrogating Doppler wave. This is known as the Nyquist limit ($F = PRF/2$). A simple visual analogy of this concept is the moving wagon wheel in a motion picture. If the frame speed is at least twice that of the moving wagon wheel, it will appear to be moving in a clockwise direction. However, if the film speed is less than half of the wagon wheel, it will appear to be going backwards. In Doppler

echocardiography, the term for the ambiguity in assessing the returning signal that results from frequencies above the Nyquist limit is called “aliasing” (Otto, 2000).

Continuous wave Doppler avoids maximal velocity limitations by continuously sending and receiving signals with the use of two crystals. Returning signals produced by pulsed wave Doppler can be reflected through the emitting beam path causing shadowing to occur. Therefore, continuous wave Doppler is used when interrogating high velocity flow along the beam path. The ability to distinguish the direction of the blood flow is also possible. Color flow Doppler provides the direction of the blood flow; red indicates flow towards the transducer and blue indicates flow away from the transducer.

Doppler flow studies have also been shown to be a sensitive means for assessing cardiac output (Lake, 1990c; Otto, 2000; Troianos, 2002). These studies are accomplished by analyzing the flow velocity across the mitral or aortic valve, the left ventricular outflow tract (LVOT), or the main pulmonary artery. A review article by Skiles suggests that calculations based on pulsed-wave Doppler flow through the LVOT demonstrates the most accurate assessment of cardiac output when compared to the thermodilution technique (Skiles, 2000). By acquiring the velocity of blood flow across the LVOT, for example, a velocity-time interval (VTI) is derived. Conceptually, the VTI represents the cumulative distance, commonly referred to as the “stroke distance”, that the red blood cells travel during the systolic ejection phase. The VTI is multiplied by the cross-sectional area (CSA) of the LVOT to derive the blood flow velocity, which is analogous to stroke volume (in cubic centimeters). Cardiac output, therefore, can be obtained by multiplying the stroke volume times the heart rate.

$$C.O. = \pi r^2 (TVI) \times H.R.$$

Several studies support the use of Doppler flow for the assessment of cardiac output. In a study by Stoddard and colleagues of 28 consecutive ICU patients, a strong correlation was found between cardiac output derived from Doppler flow velocities in the LVOT with TEE both in the transverse ($r = 0.97$) and longitudinal ($r = 0.95$) planes of image acquisitions and thermodilution with the pulmonary artery catheter (Stoddard, Prince, Ammash, Goad, & Vogel, 1993). Perrino and colleagues in their study of 33 patients undergoing coronary artery bypass grafting reported similar results. An equally strong correlation ($r = 0.98$) of cardiac output between Doppler by TEE and thermodilution with the pulmonary artery catheter was demonstrated in their interrogation of the LVOT in 32 of 33 (97%) patients (Perrino, Harris, & Luther, 1998). These authors concluded that TEE Doppler in the transgastric view provided an alternative method to cardiac output determination with minimal movement of the TEE probe. This is a significant point since most practitioners prefer the transgastric short axis view for global assessment of left ventricular function and volume status.

Interestingly, research by Muhiudeen and colleagues at the University of California San Francisco found a modest correlation of cardiac output between Doppler flow analysis of the pulmonary artery and thermodilution by pulmonary artery catheter ($r = 0.65$). Minimal correlation was reported between Doppler flow analysis of the mitral valve and thermodilution ($r = 0.24$) (Muhiudeen, Kuecherer, Lee, Cahalan, & Schiller, 1991). These researchers concluded that, in their series of 35 cardiac surgical patients, pulsed wave Doppler interrogation of the mitral valve and pulmonary artery was of limited ability in determining cardiac output when compared to the thermodilution technique.

In contrast, intraoperative Doppler interrogation of valvular function has become a standard procedure provided by the cardiac anesthesiologists during cardiac surgery for valve replacement or repair and is documented in many echo textbooks (Lake, 1990c; Otto, 2000; Troianos, 2002). Likewise, the assessment of regurgitant valvular flows can be estimated, as can intracardiac pressures and gradients through septal defects. Although this author has had minimal experience in this area of echocardiography and it is usually not a part of volume assessment in the critically ill patient, it is an important aspect of echocardiography and an overview will be provided.

Regurgitant volumes can be calculated by subtracting the forward flow of the reference valve from the forward flow through the regurgitant valve. That is, if the regurgitant valve is the mitral and the reference valve is the aortic (without significant disease), the regurgitant volume would be:

Regurgitant Volume_{MV} = forward flow through mitral valve - forward flow through aortic valve

The regurgitant volume can also be measured with the same calculation if the aortic valve were incompetent:

Regurgitant Volume_{AV} = forward flow through aortic valve – forward flow through mitral valve

The regurgitant fraction is a ratio of the regurgitant volume to the total forward flow and is expressed as a percentage:

Regurgitant fraction (%) = regurgitant volume /total forward flow

Intracardiac shunts are a ratio of pulmonic to systemic stroke volume (Q_p/Q_s) and can be assessed by calculating the stroke volume of the LVOT (or aortic valve) and the RVOT (or pulmonary artery):

$$Q_p/Q_s = SV_{\text{Right Heart}} / SV_{\text{Left Heart}}$$

These measurements are generally used for assessment of congenital heart lesions and are often combined with color Doppler examinations to provide a complete cardiac evaluation (Maslow, 2003b).

Intracardiac pressure gradients are often used to estimate intracavitary pressures in the assessment of valvular disease (e.g., aortic stenosis), septal defects, outflow tract abnormalities, and major vessel pathology. Increases in blood flow velocity occur through a stenotic lesion and this velocity is proportional to the degree of narrowing. The relation of blood flow velocity through a narrow orifice is described in the Bernoulli equation (Maslow, 2003b):

$$\Delta P = \underbrace{1/2\rho(v_2^2 - v_1^2)}_{\text{Convection acceleration}} + \underbrace{\rho(dv/dt)dx}_{\text{Flow acceleration}} + \underbrace{R(v)}_{\text{Viscous friction}}$$

where P is the pressure gradient across the area of interest (mmHg), ρ is the density of blood ($1.06 \times 10^3 \text{ kg/m}^3$), v_1 is the peak velocity of blood flow proximal to the area of interest (m/s), and v_2 is the peak velocity of blood flow across the area of interest (m/s).

In clinical practice, the Bernoulli equation is simplified by ignoring flow acceleration, viscous friction, and the velocity proximal to the area of interest (v_1) (Maslow, 2003b; Otto, 2000). The rationale for ignoring these effects is because:

1. Flow acceleration: The peak flows are of interest to the clinician and during the peak flow, flow acceleration is non-existent.

2. Viscous friction: The viscosity of blood is significant only in small orifices of $<0.25\text{cm}^2$. Since blood flow is thought to be constant through orifices greater than this measurement, the friction associated with clinically significant stenotic orifices are large enough to also eliminate this portion of the equation.
3. In clinical practice, stenotic lesions are thought to have a substantially greater peak velocity across the area of interest than the peak velocity proximal to the stenosis, such that $v_2^2 - v_1^2$ can be approximated by just v_1^2 .

With the elimination of these portions of the equation, a simplified Bernoulli equation is produced:

$$\Delta P = 4 v_2^2$$

Therefore, a more convenient calculation for estimating the pressure gradient can be obtained by measuring the peak blood flow velocity across the lesion of interest, which is diagrammatically shown in Figure 2.4.

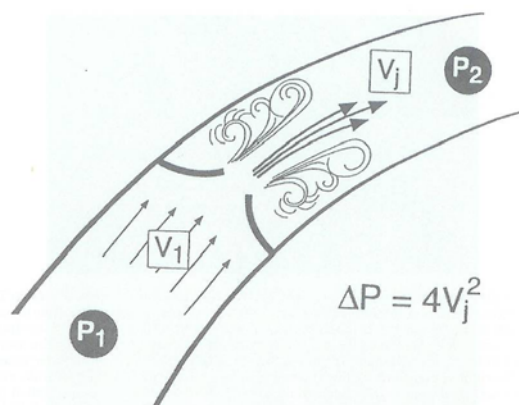


Figure 2.4. The simplified Bernoulli equation states the change in pressure across a stenotic orifice ($P_2 - P_1$) is four times the square of the high-velocity jet. P_1 is the pressure proximal to the stenosis, V_1 is the velocity proximal to the stenosis, P_2 is the pressure distal to the stenosis, V_j is the jet flow through the stenotic valve. From Maslow and Perrino, Chapter 6: Quantitative Doppler and Hemodynamics, In: Perrino and Reeves, *A Practical Approach to Transesophageal Echocardiography*, 2003, p. 100, with permission.

Pressure gradients are calculated from images obtained by either pulsed or continuous wave Doppler sampling across the region of interest (Maslow, 2003b). The

measured peak velocity is inserted into the simplified Bernoulli equation to estimate the pressure gradient. To avoid aliasing, continuous wave Doppler is used if the blood flow velocity is $>1.4\text{m/s}$. It is important to place the Doppler beam so that the jet with the highest velocity is interrogated. This will assure that there is no underestimation of the pressure gradient evaluation. Multiple flow profiles are also advocated to ensure accuracy of the estimation (3-5 for regular rhythms and 10 for irregular rhythms). The simplified Bernoulli equation is the basis for most pressure gradient calculations in clinical echocardiography.

Trans-mitral Doppler Flow in Volume Analysis

No data are reported comparing changes in volume and cardiac chamber dimensions with corresponding changes in trans-mitral Doppler flow velocities characteristics. The evaluation of left ventricular diastolic function is considered an important independent component of overall cardiac performance (Otto, 2000). Diastolic dysfunction is significantly relevant in those patients with congestive heart failure. It is defined clinically as an impairment of the ventricles to fill at their usual low pressures and commonly involves abnormalities in ventricular relaxation or chamber compliance (Shernan & Zile, 2003). Although the PAC is useful in assessing global cardiac performance, it is unable to directly measure left ventricular pressure and volume or trans-mitral flow. Echocardiography, however, is capable of evaluate these indices. The trans-mitral Doppler flow velocity is obtained by placing the TEE probe in the mid-esophageal four-chamber view and aligning the pulsed-wave Doppler sample volume at the tip of the mitral valve leaflets (Shernan & Zile, 2003). A normal biphasic flow pattern is shown below in Figure 2.5.

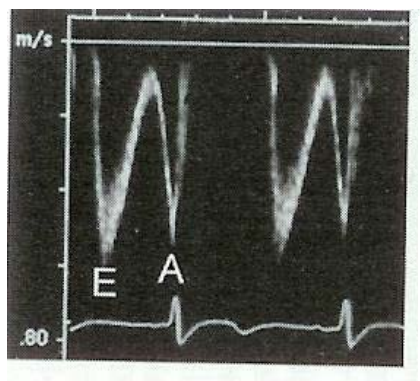


Figure 2.5. Pulsed wave Doppler (normal). From: Perrino and Reeves, 2003, with permission.

The initial peak flow velocity of ventricular filling (E-wave) occurs during early diastolic filling and is followed by a later peak flow velocity (A-wave) that is caused by left atrial contraction. The period between the two waves is called the “diastasis” and is characterized by minimal blood flow. As the left ventricle becomes more dependent on the atrial contraction component for additional filling, peak flow changes occur with the A-wave becoming more prominent as demonstrated Figure 2.6 below.

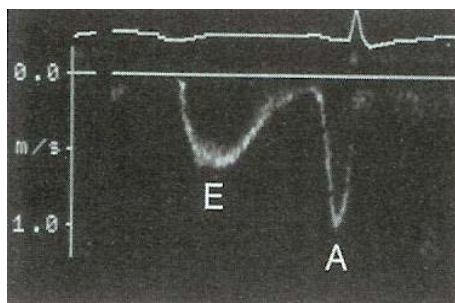


Figure 2.6. Pulsed wave Doppler (abnormal). From: Perrino and Reeves, 2003, with permission

The pressure gradient between the left atrium and ventricle determines the Doppler trans-mitral blood flow velocity, which depends on several variables that include heart rate and rhythm, atrial contractility, early filling loads, mitral valves disease, ventricular septal pathology, and ventricular compliance (Otto, 2000; Shernan & Zile, 2003). Normal aging can also cause delayed left ventricular relaxation resulting in a lower initial trans-mitral pressure gradient (Shernan & Zile, 2003). Computer software can calculate the various

indices that provide information regarding trans-mitral flow velocities, including E-wave / A-wave (E/A) ratios, time/velocity integrals (TVI_E , TVI_A), and deceleration time (DCT-E, DCT-A), which are depicted in Figures 2.7 and 2.8 below.

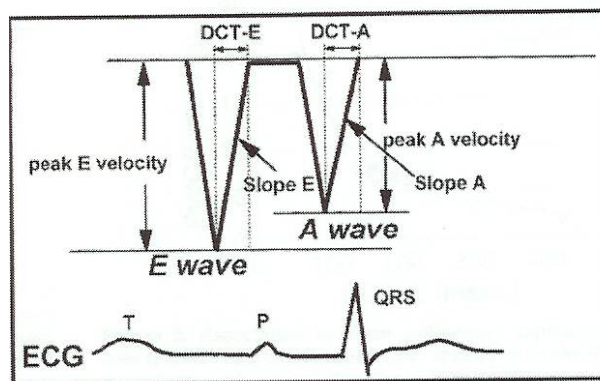


Figure 2.7. E and A-wave measurement characteristics. From: Nomura M, et al., *Anesthesia and Analgesia*, 1997, with permission.

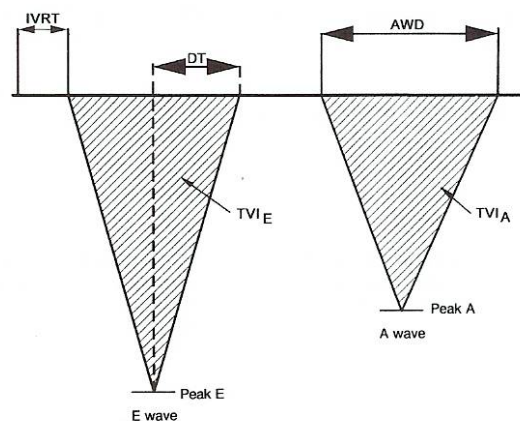


Figure 2.8. E and A-wave measurements. From: Perrino and Reeves, 2003, with permission

IVRT indicates the isovolumic relaxation time, which refers to the time from the end of ventricular outflow and the beginning of ventricular inflow (Mohrman, 2003). IVRT occurs just prior to the early passive left ventricular flow (E-wave) and is also affected by diastolic dysfunction. A shortened IVRT (<60 ms) indicates premature mitral valve opening, which can indicate elevated left ventricular pressure. Conversely, a lengthening of the IVRT (>110 ms) suggests impaired left ventricular relaxation and results in a delayed mitral valve opening (Shernan & Zile, 2003). In addition, the E-wave

deceleration time (DCT-E) has been shown to have a strong correlation with PAOP ($r^2 = 0.89$) (Nomura, Hillel, Shih, Kuroda, & Thys, 1997).

The E/A wave ratio has been shown to be a sensitive indicator of changes in preload and cardiac output. Lattik and colleagues at the Montreal Heart Institute in Quebec investigated the response of 36 cardiac surgical patients to a rapid intravascular infusion of a 500ml bolus of 10% pentastarch (Lattik et al., 2002). E/A ratio determined from trans-mitral Doppler flow predicted the increase in cardiac output as a result of increased preload. This is clinically relevant because E/A ratios determined by trans-mitral Doppler flow may identify patients who are likely to benefit from volume administration with an improvement in cardiac output and might identify those patients who are at risk for an adverse response. Lattik and his co-investigators (2002) demonstrated that the lower the initial E_{TVI}/A_{TVI} ratio, the more likely that an increase in cardiac output would result from an expansion in preload.

The Evolution of Intraoperative Transesophageal Echocardiography

Transesophageal echocardiography (TEE) has been providing intraoperative cardiac assessment for more than twenty years. Its roots are well established in cardiac surgery where cardiac anesthesiologists were the first to use TEE technology. The technology dates back to the first m-mode transesophageal echocardiograph in 1976 when researchers attempted to have patients swallow a small epicardial echo probe (Frazin, 1976). This was followed by the first crudely fashioned TEE probe made from an epicardial echo probe reinforced with sternal wire and wrapped in an esophageal stethoscope that was used for continuous cardiac monitoring of left ventricular function during cardiac surgery (Matsumoto, 1980). The first two-dimensional phased-array

transducer was mounted on the tip of a flexible gastroscope in 1982 at the University of Hamburg (Schluter, 1982). This development significantly enhanced the ability of TEE to assess a two-dimensional image of the heart. The mid-1980s also saw TEE technology advance to the point where doubling the number of crystal elements in the probe (piezoelectric crystals) improved the power of the transducer to create high-resolution cardiac images (Lancee, 1988). The additional advancement from biplane to multiplane image acquisition enhanced the transducer's capability to interrogate cardiac structures and blood flow. These improvements led to the use of the TEE for intraoperative assessment of the heart during cardiac surgery (Cahalan et al., 1987; Cahalan, Lurz, & Schiller, 1988).

Two decades after its introduction for intraoperative assessment and management of cardiac patients, TEE is now recognized as an integral part of intraoperative management in patients undergoing a number of high-risk surgical procedures. Indications for the use of intraoperative TEE have been documented in practice guidelines developed by the American Society of Anesthesiologists and the Society of Cardiovascular Anesthesiologists (Thys, 1996).

These guidelines provided the first evidence-based justification for intraoperative echocardiography and summarized the recommendations and indications for intraoperative TEE. In addition, the guidelines identify various clinical situations where TEE monitoring could provide important hemodynamic and cardiac structural information. Among these is the ability of TEE to assess hemodynamic function, left ventricular wall motion, and myocardial ischemia. TEE is also used to assess valvular function, patients with congenital heart defects, and intraoperative assessment of wall

motion during coronary artery bypass surgery. Other clinical uses of TEE that did not have strong scientific evidence were the evaluation of cardiomyopathy, cardiac aneurysms and tumors, and the detection of foreign bodies and air emboli.

In these guidelines are three categories that list the indications for the use of TEE that are supported by either clinical evidence or expert opinion, which are listed in Appendix 1. Category I indications are evidence-based and supported with expert opinion. Category II indications have weaker evidence to support its use, has expert consensus and is representative of clinical indications where TEE may be useful in improving outcome. Indications in Category III have little current scientific or expert support and do not appear to significantly improve clinical outcome. While most of the indications in the three categories identify cardiac patients undergoing either cardiac surgery or non-cardiac surgical procedures, other clinical situations where TEE is indicated are documented. Three perioperative indications where TEE is frequently useful in improving clinical outcome are recognized in Category I. These include intraoperative evaluation and determination of ventricular function in patients exhibiting acute, persistent, and/or life-threatening hemodynamic disturbances that have not responded to treatment. Two other perioperative situations that are described in Category I are the preoperative evaluation of the unstable patient with a suspected thoracic aortic aneurysm/dissection and the evaluation of an unexplained hemodynamically unstable patient in the Intensive Care Unit whose etiology cannot be determined by other monitoring techniques such as vital signs or readings from the pulmonary artery catheter.

Supported by weaker evidence and expert consensus, Category II lists intraoperative situations other than those related to cardiac surgery. One is the

intraoperative detection of foreign bodies in the heart or great vessels. The other clinical situation is the intraoperative evaluation of the heart for possible damage associated with either sharp (gunshot or knife wound) or blunt (motor vehicle accident) trauma.

Category III lists indications with little scientific or expert support. Of the nine clinical situations in this section, one is outside of the more common cardiac surgical indications. Intraoperative monitoring during orthopedic procedures for the possibility of emboli is infrequently used to identify patients who might have an undiagnosed patent foramen ovale. This anomaly has a high risk of allowing thromboemboli entering the right atrium to easily migrate into the left atrium and causing a stroke.

Although the guidelines acknowledge the lack of concrete evidence and identify limitations with intraoperative TEE use such as drawing attention from the actual patient care responsibilities and difficulties with image acquisition, the authors agree that TEE may provide a more accurate estimate of left ventricular preload compared to the pulmonary artery catheter.

This Task Force also agreed that hemodynamic function could be assessed by TEE in a more expedient manner because, unlike the pulmonary artery or central venous catheters, it does not require sterile technique for insertion and is less invasive. Finally, a more global hemodynamic profile of cardiac performance and a rapid assessment of cardiac anatomical structures are possible with TEE compared to invasive catheter placement.

In 1999, a position paper published by the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists described the consensus guidelines for performing a comprehensive TEE examination of the heart and great vessels. Also

included in this position paper were accepted standardized nomenclature for describing echocardiographic views and probe positioning (Shanewise et al., 1999). The comprehensive examination is comprised of 20 cross-sectional views of the heart and great vessels that is illustrated in Figure 2.9 below. This examination is now considered the standard in TEE assessment of the heart and is referred to in echocardiography texts (DiNardo, 1998; Otto, 2000; Troianos, 2002).

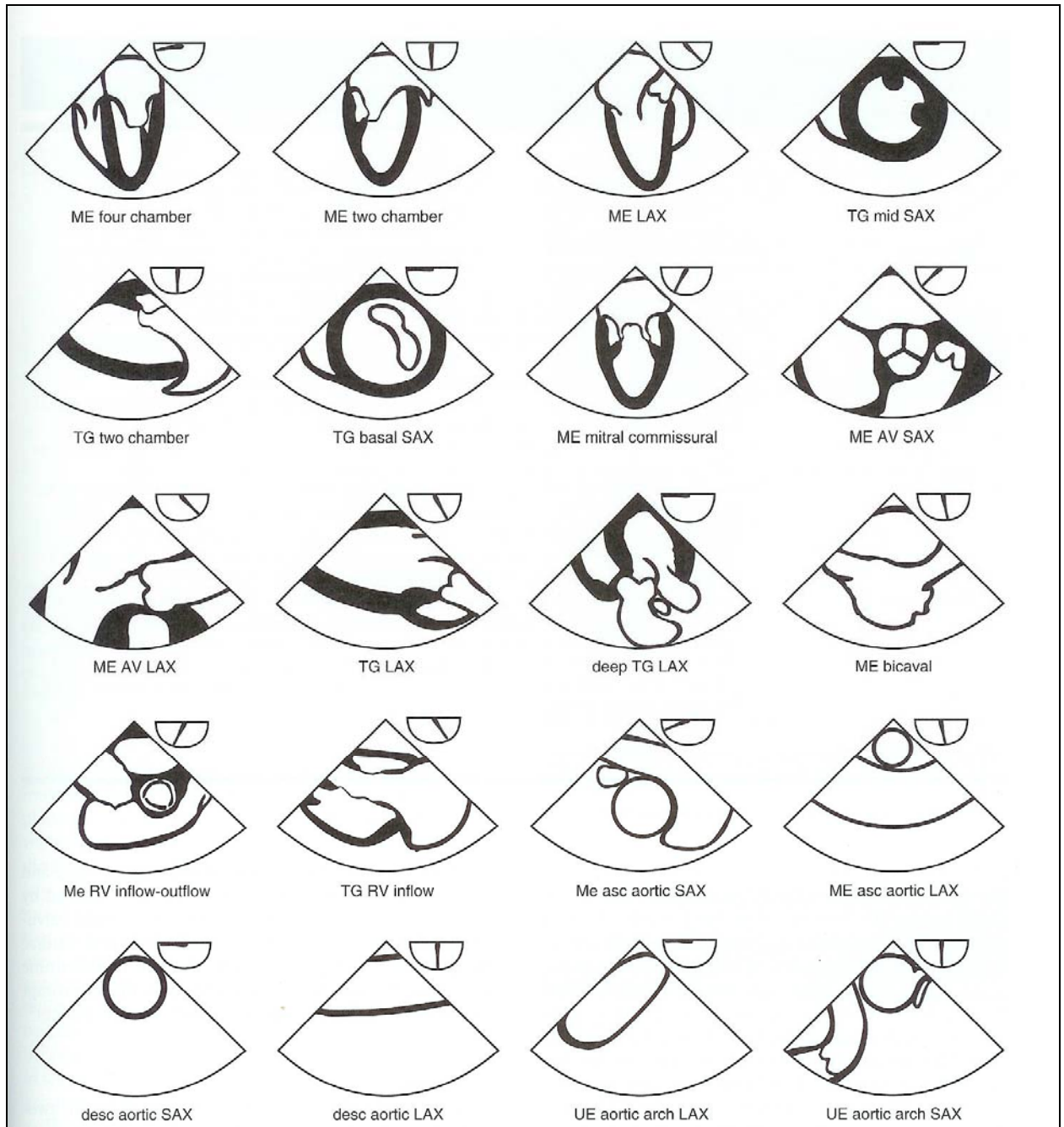


Figure 2.9. The recommended 20 cross-sectional views that make up the comprehensive TEE examination. The icon to the right of the view indicates the approximate multiplane angle of the transducer. asc: Ascending; AV: aortic valve; desc: descending; LAX: long axis; ME: mid-esophageal; RV: right ventricle; SAX: short axis; TG: transgastric; UE: upper esophageal. From Shanewise JS, et al, *AnesthAnalg*, 1999, p. 874, with permission.

In addition to the comprehensive TEE examination, the position paper provided the recommendations for the assessment of left ventricular wall motion, which will be discussed in later sections of this paper, and interrogation of the left and right atria, cardiac valves, the left ventricular outflow tract, pulmonary artery, coronary sinus, and the pulmonary veins. These guidelines were instrumental in establishing TEE as a reliable intraoperative clinical monitor in cardiac surgery.

In 2002, another task force of the American Society of Echocardiography and the Society of Cardiovascular Anesthesiologists was created to review the earlier 1996 guidelines and update the requisite training for those practitioners who perform consultative perioperative echocardiography (Cahalan et al., 2002). The guidelines document the goals and objectives that need to be achieved (Appendix 3).

Under the section entitled, “Prerequisite Medical Knowledge and Training”, the guidelines state that the trainees in perioperative echocardiography must be “licensed physicians enrolled in, or having completed, an accredited residency” (p. 648). This recommendation is significant since this practitioner is not a physician. However, the important point that must be made is that the focus of this author’s previous training, both didactic and practical, is not to provide perioperative consultative services, but to develop personal knowledge and application of transesophageal echocardiography. In addition, this author practices as a nurse anesthetist in an academic level I trauma center where the philosophy of perioperative anesthesia management is provided through an anesthesia care team. This anesthesia care team consists of an anesthesiologist and a nurse anesthetist who work collaboratively in the administration of the anesthetic. Therefore,

when TEE is used, it is always under the guidance of a physician (anesthesiologist) who is credentialed in echocardiography.

The training guidelines also identify the basic and advanced training components (p. 648-651) and the number of examination that should be performed to achieve a basic or advanced level of experience. Since this practitioner works with an anesthesiologist as described above and is not planning on independent intraoperative consultative TEE, the basic minimum numbers of 150 examinations with 50 personally performed are not as important as the ability to attain both the cognitive and technical skills listed in Appendix 3. The author's basic training recommendations are being met at this time through study and hands-on work at the University of California Davis Medical Center (UCDMC) with the cardiac anesthesiologists.

A Review of the Invasive Methods for Assessing Intravascular Volume and Preload

The ability to monitor and assess the heart's filling capacity is an important aspect of perioperative critical care. This filling capacity, recognized as the concept of preload, is defined as the volume of blood in the ventricle at the end of diastole (end-diastolic volume or EDV) that is delivered with each ventricular contraction. It is assumed that both ventricles deliver equal volumes of blood in a normally functioning heart. The left ventricle is responsible for systemic oxygen delivery and is enveloped by a more muscular wall that results in higher systolic pressures (Lake, 1990b). Knowledge of the amount of blood that is ejected from the heart with each contraction provides valuable information regarding cardiac function as well as intravascular volume. Information regarding cardiac preload and contractility guides volume replacement during resuscitation of critically ill patients, especially the trauma patient.

Before the development of echocardiographic technology, practitioners used pressure measurements to assess ventricular preload in the forms of central venous pressure (CVP) and later with pulmonary artery pressure (PAP) and pulmonary artery occlusive pressure (PAOP), formerly referred to as pulmonary artery wedge pressure (PAWP). The use of pressure measurements to evaluate left ventricular preload relies on the assumption that there is no cardiac pathology (valvular disease) between the catheter tip and the left ventricle. Any obstruction or dysfunction (pulmonary vascular disease) between the left ventricle and the point where the measurement is taken (vena cava with the CVP and pulmonary artery with the PAP) will influence the numerical data received by the pressure transducer (Lake, 1990b).

Since it is technically difficult to obtain direct ventricular volumetric measurements, the pressure readings received from the central venous and pulmonary artery catheters are used to estimate these ventricular volumes. These traditional monitoring capabilities have been enhanced to include the continuous measurements of cardiac output and mixed venous oxygen saturation and the ability to derive right ventricular stroke volume to estimate left ventricular volume. The use of right ventricular volumes obtained by the Right Ejection Fraction (REF) pulmonary artery catheter to quantify left ventricular volume has been shown to actually overestimate left ventricular preload when compared with the TEE. In their prospective study of 30 mechanically ventilated surgical ICU patients, Kraut and colleagues found that the RVEDV measured with the REF pulmonary artery catheter significantly overestimated LVEDV (LV preload) by a factor of 2 (Kraut, Owings, Anderson, Hanowell, & Moore, 1997). The authors warned that guiding volume resuscitation by indirect pressure measurements

might lead to a false sense of security and result in the overestimation of LV preload and therefore under-resuscitation of the patient.

The literature also supports the notion that pressure measurements as a guide to volume assessment and replacement is affected by the fundamental cardiac muscle preload forces originally described by Otto Frank in 1894 and formally documented by E. H. Starling in 1918 to form what is now referred to as the Frank-Starling law of the heart. Stroke volume is increased as cardiac preload or end-diastolic volume is increased. Physiologically, the additional stretch of the cardiac muscle fiber is from the augmented preload allowing for more actin and myosin contraction coupling (Figure 2.10) which increases the force of the contraction and leads to increased stroke volume (Boulpaep, 2003a; Mohrman, 2003).

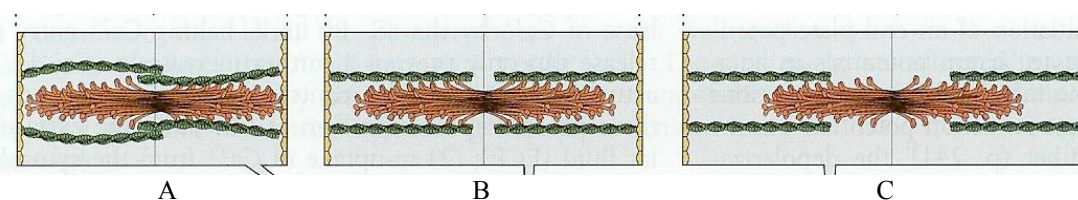


Figure 2.10. A diagrammatic representation of the actin-myosin contraction apparatus (sarcomere) in a shortened (A), optimal (B), and over-expanded (C) position. B represents an optimal contraction potential with all actin-myosin available for contraction. A is shortened due to decreased preload and shows a fold in the actin (green) filament. C illustrates distention of the actin-myosin fibers with some myosin heads unavailable for contraction. From: Baron and Boulpaep, *Medical Physiology*, 2003, with permission.

As the fiber stretch continues with larger end-diastolic volumes, a point is reached where increasing the preload does not result in an increase in stroke volume (Figure 2.11).

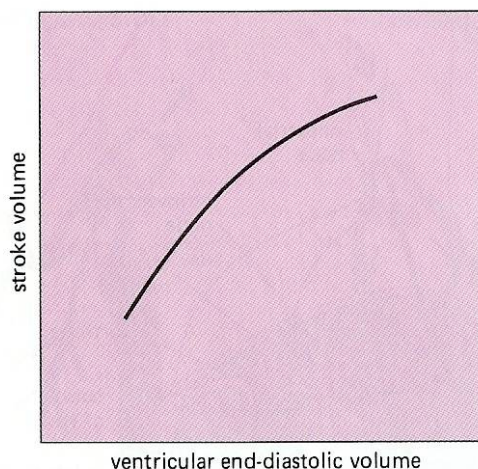


Figure 2.11. The Frank-Starling law of the heart. From Mohrman and Heller, *Cardiovascular Physiology*, 2003, p. 12, with permission.

At this point the cardiac muscle fiber has reached its maximal effective stretch and any additional increase will actually lead to a decrease in stroke volume (Boulpaep, 2003a; Mohrman, 2003). The measured effect with the CVP, and especially with the PAC, will be an increasing pressure with a concurrent decrease in stroke volume. As the cardiac muscle fiber length reaches its maximal stretch, small changes in volume will result in large increases in pressure. Increasing volume greater than this amount will result in a decreased stroke volume and increasing PAOP. Physiologically, this is due to the cardiac muscle stretched beyond the effective actin-myosin contraction coupling capabilities characterized by the drop in the Frank-Starling curve (Lake, 1990b).

Morbidity Associated with Invasive Monitoring Techniques

Concerns regarding the safety profile of invasive intravascular monitoring devices like the pulmonary artery catheter have led some investigators to scrutinize its use. A recent review by Polanezyk and colleagues of patients who underwent right heart catheterization for non-cardiac surgery discovered a three-fold increase in the incidence of major cardiac and non-cardiac morbidity (Polanezyk, 2001). These complications

included major cardiac events (myocardial infarction and unstable angina), congestive heart failure, and significant non-cardiac morbidity (bacterial pneumonia, pulmonary embolism, non-cardiac pulmonary edema, respiratory failure requiring intubation, renal failure requiring dialysis, cerebrovascular accident, and gastrointestinal bleeding).

Similar safety concerns have been reported by the Anesthesia Patient Safety Foundation and others regarding a higher incidence of nosocomial infections and other catheter related morbidity (Ali, Omran, Rakowski, & William, 2001; Brown, 1997; Truman, 1997).

The economic aspects of PAC use have been debated, however the cost-effectiveness and economic impact of its use is not well established. Chalfin reported that, although intensive care units account for 5%-10% of the inpatient beds, they consumed more than 30% of the hospital budget (Chalfin, 1997). He also estimated that over one million pulmonary artery catheters were inserted every year leading to a cost in excess of \$2 billion dollars. He concluded by writing, “the economic impact and cost-effectiveness are moot prior to establishing clinical efficacy” (p. 292). There is some question as to whether the PAC improves patient outcome even when there are no complications (Connors, 1997; Connors et al., 1996) despite the fact that others have shown a statistically significant reduction in clinical morbidity with PAC-guided therapy. While a need for large randomized controlled trials (RCT) are advocated, Ivanov and colleagues reported in a meta-analysis of 16 RCT’s (n = 1610), a statistically significant decrease in morbidity (p = .017) in patients whose treatment was guided by pulmonary artery catheter measurements (62.8%) as compared to those patients who did not have a PAC (74.3%) (Ivanov, Allen, & Calvin, 2000). More recently, Sandham and colleagues

performed a randomized controlled trial of 1994 critically ill elderly (>60 years) surgical patients where goal-directed therapy with PAC was compared to standard ICU care without the PAC (Sandham et al., 2003). The authors reported no differences in hospital mortality (7.8% with PAC and 7.7% without PAC). Survival rates at six months were 88.1% in the standard group compared to 87.4% in the PAC group. Survival rates at one year were 83.9% in the standard group and 83.0% in the PAC group. The researchers did report eight incidents of pulmonary embolism in the PAC group compared to none in the standard care group ($p = .004$) and concluded that no benefit was observed with therapeutic-directed PAC compared with standard care in elderly surgical patients. In a similar study by Harvey and colleagues performed a randomized controlled trial of 1014 ICU patients in 65 Intensive Care Units in the UK (Harvey et al., 2005). Pulmonary artery catheters were placed in 519 patients while 522 patients were managed without the use of a PAC. Hospital mortality was 68% in the PAC group and 66% in the non-PAC group ($p = .39$). Forty-six patients in the PAC group were noted to have non-fatal complications. These authors also reported no benefit or harm with the PAC use in critically ill patients. Finally, in a recent review article Bundgaard-Nielsen and colleagues suggested that early placement of the PAC may be an important factor in maximizing the goal-directed therapy and management of the critically ill patient (Bundgaard-Nielsen, Holte, Secher, & Kehlet, 2007).

These questions and concerns regarding invasive monitoring enhanced an already growing interest in the use of transesophageal echocardiography as a relatively non-invasive method for the assessment of cardiac function and filling in the perioperative patient population. Presently, transesophageal echocardiography is an established

technique for the assessment of global left ventricular function, cardiac output, and anatomical structural assessment (Brown, 2002; Cheung et al., 1994; DiNardo, 1998; Lake, 1990c; Otto, 2000; Tousignant, 2000; Troianos, 2002; Wolrab et al., 1997). These characteristics will be reviewed in the following sections.

Evaluation of Global Left Ventricular Function

The assessment of left ventricular performance is an integral part of echocardiography's examination of the heart. Two important aspects of this evaluation are the left ventricular (LV) filling volume or preload conditions and LV regional wall motion. Both of these features have a significant impact on the ability of the heart to maintain adequate cardiac output for the steady supply of oxygen to and removal of waste products from the cells of the body.

The estimation of LV filling or preload is achieved by the quantification of left ventricular end-diastolic dimensions. The two techniques for estimating preload are based on left ventricular diameter, which supplies a one-dimensional approximation or left ventricular area, which provides a two-dimensional estimation of a three-dimensional volume. By measuring both the end-diastolic and end-systolic dimensions, ejection phase indexes can be calculated. These estimations are considered a standard component of LV assessment and are described in TEE textbooks (Lake, 1990c; Otto, 2000; Troianos, 2002).

Fractional shortening (FS), a one-dimensional view of the heart, is a simple method for quantifying LV systolic function and is the percentage of change in LV cavity dimension with systolic contraction. It is expressed in the formula:

$$FS = \frac{EDD - ESD}{EDD}$$

End-diastolic End-systolic
diameter diameter

These measurements are performed either in the m-mode or with two-dimensional echocardiography at the chordae below the level of the mitral valve and perpendicular to the long axis of the left ventricle. The normal range of fractional shortening that is found in echocardiography textbooks is between 25% and 45% (Otto, 2000; Troianos, 2002; Walton, 2003). This one-dimensional measure is a simple and quick method for obtaining the ejection fraction. Its limitation is that it uses one image view that provides a single cavitory dimension in systole and diastole to reflect the global LV function. This may be acceptable in patients with normal LV function, but can present erroneous data in those with abnormal LV performance such as dilated cardiomyopathy or regional wall motion abnormalities.

Fractional area change (FAC) and automated border detection (ABD), obtained from two-dimensional images of the heart, is a surrogate index of LV volume. The use of FAC, either with manual planimetry or automated border detection, to estimate LV volume is due to the fact that echocardiographic calculations are complex and time consuming (discussed later). The established standard view for estimating fractional area change is obtained with the TEE placed in the trans-gastric short-axis position at the level of the papillary muscles (Otto, 2000; Troianos, 2002). FAC is determined by the formula:

$$\text{FAC} = \frac{\text{EDA} - \text{ESA}}{\text{EDA}}$$

End-diastolic End-systolic
area area

The images are freeze-framed in both diastole and systole and planimetry of the endocardial borders are performed (Figure 2.12). Established normal values for FAC are between 50% and 75% and equate with ejection fraction (Otto, 2000; Walton, 2003).

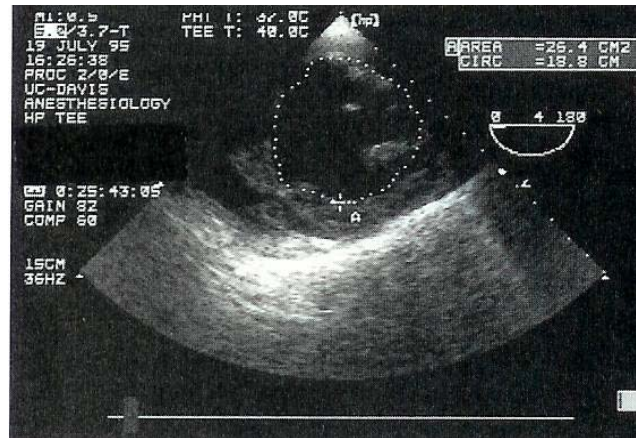


Figure 2.12. Two-dimensional TEE image of the left ventricle in the transgastric short axis view with the left intraventricular border outlined in end diastole with planimetry. From: Hanowell, LH, 1998, p. 255, with permission.

Acoustic quantification (AQ) is an automated method for obtaining FAC and provides a real-time assessment of ventricular preload. The automated border detection technique uses acoustic information through boundary detection algorithms, within the TEE software, that differentiates echocardiographic signals between the myocardium and blood interface. After the region of interest is defined via a manual tracing of the LV chamber in the trans-gastric short axis view, automated border detection estimates beat-to-beat assessment of EDA, ESA, and FAC (Figure 2.13). In a review article by Hanowell and colleagues, the computations generated with ABD are considered analogous to those of fractional shortening and ejection fraction (Hanowell, 1998).

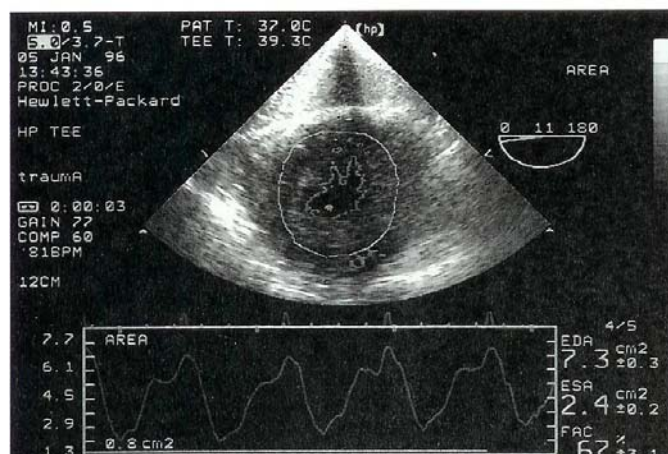


Figure 2.13. Continuous TEE monitoring of the left ventricular area using acoustic quantification technology. From: Hanowell, LH, 1998, p. 256, with permission.

In a study at University of California San Francisco (UCSF), Cahalan and colleagues retrospectively examined 25 cardiac surgical patients to compare ABD's online real-time calculations of ESA, EDA, and FAC to the off-line manual planimetry measurements. The results indicated that ABD slightly underestimated EDA and slightly overestimated ESA. In addition, ABD underestimated FAC. The authors concluded that when ABD is adequately performing, it underestimates LV FAC, however, it does provide valid real-time estimates of LV EDA and LV ESA (Cahalan, 1993). In a follow-up study by Perrino and associates at Yale University, these authors designed a prospective investigation to evaluate the accuracy and trending capability of ABD compared to off-line manual planimetry of EDA, ESA, and FAC. Their results indicated a strong correlation of LVEDA ($r = 0.89$), LVESA ($r = 0.93$), and FAC ($r = 0.90$) between ABD and off-line manual planimetry. These correlation data appear to coincide with the estimation data reported by Cahalan. The authors also reported a 96% accuracy rate in ABD's ability to track serial changes in LV area with a sensitivity of 83% and specificity of 85% for detecting acute changes in LV area (Perrino et al., 1998). Marcus and colleagues from the University of Chicago reported similar results in their study of

18 subjects when they compared ABD to ultra-fast computed tomography. Strong correlation between ABD and CT measurements of EDA ($r = 0.99$), ESA ($r = 0.93$), and FAC ($r = 0.91$) were similar to those reported by Perrino and associates (Marcus et al., 1993). These authors also reported that ABD slightly underestimated both EDA and FAC and overestimated ESA. These findings are consistent with those of Cahalan and colleagues. All of the authors agree that ABD is dependent upon quality 2-D images for accurate assessment and alterations in the gain sensitivity during the cardiac cycle interfere with image quality. This is especially true in the resolution of the lateral images created by TEE during the cardiac cycle (Skiles, 2000).

More quantitative measurements of left ventricular dimensions are available and require two-dimensional LV views to provide tomographic measurements of length and area. These images require clear endocardial border definition in both end-systole and end-diastole. After obtaining these 2-D measurements, they are then applied to geometric models to estimate three-dimensional cavity volumes (Walton, 2003). The techniques described are time consuming and are not usually part of the TEE evaluation of critically ill patients. They are most often used in cardiac catheterization or electrophysiology laboratories. Their discussion here is for completeness of the topic.

Obviously, the use of two-dimensional measurements to calculate and obtain three-dimensional values has its limitations. The first limitation is that an assumption must be made that the geometric structure of the heart is normal, which is generally considered to be a prolate ellipse (Otto, 2000). The problem is that normal hearts can vary significantly in their geometry.

The second limitation is that some formulas require that the TEE values obtained be cubed, which can enlarge any error in measurement. Lastly, the more images and measurements that are needed for the calculations, the more time consuming and, therefore, the less practical it is in a dynamic environment like the operating room or ICU.

A number of formulas are available to calculate LV volume (Otto, 2000; Walton, 2003). The most common are described in order of simplicity.

1. Cubed Formula ($V = D^3$): This is the simplest quantitative formula and allows one measurement to be taken in systole and diastole. The assumption made in this measurement is that the long axis dimension is twice that of the short axis dimension, which is a simplistic image of the prolate ellipsoid model. This is the least accurate formula and can dramatically overestimate the volume of larger ventricles, which occurs when the LV dilates along the short axis becoming more spherical in shape (Figure 2.14).

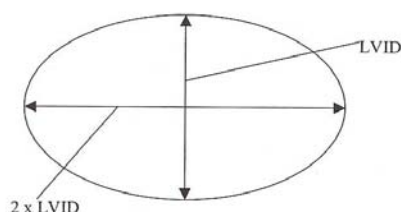


Figure 2.14. LVID: LV internal diameter.
From Perrino and Reeves, 2003, with permission

2. Single-plane ellipsoid Formula ($V = 8A^2/3\pi L$): This formula is more complex and is aided by internal software in the TEE systems. Obtaining the views is accomplished in the mid-esophageal four-chamber or two-chamber view and must completely visualize the left ventricle. Again, the assumption is made that the LV is modeled as a prolate ellipse and the entire LV is visualized. A

limitation is that this calculation does not take into consideration the volume displaced by the papillary muscles, trabeculae, and the mitral valve apparatus (Figure 2.15).

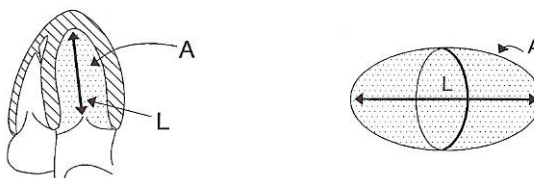
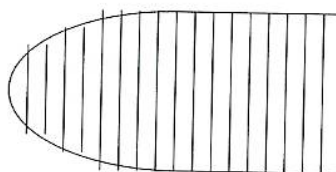


Figure 2.15. A: Area, L: Length
From Otto, 2000, with permission

3. Simpson's method of discs, Methods of discs Formula: $(V = \sum_{n=20} [Area \times (L/20)])$
This formula is quite complex and uses a series of discs (>20) from the apex to the base of the LV to calculate its volume. The calculations are now included in the software program on most TEE equipment (Figure 2.16).



$$V = \sum_{n=20} [Area \times (L/20)]$$

Figure 2.16. Modified Simpson's Method. From Perrino and Reeves, 2003, with permission

The American Association of Echocardiography advocates the use of the modified Simpson's method, which is expressed by the formula:

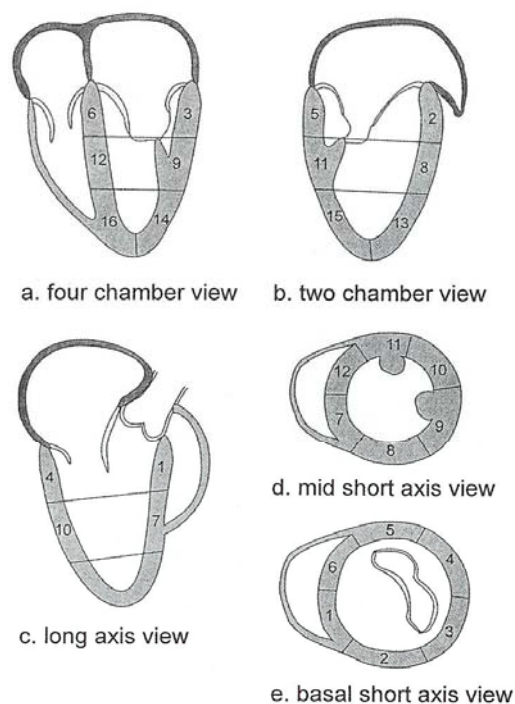
$$V = (A_1 + A_2)h + (A_3h/2) + (\pi h^3/6)$$

where A_1 is the area of the short-axis CSA at the level of the mitral valve, A_2 is the short-axis CSA at the level of the papillary muscles, A_3 is the short-axis CSA at the level of the apex, and h equals one-third the LV length (Schiller,

1989). This method of LV volume assessment is the most accurate because it incorporates multiple readings along the length of the left ventricle.

Another important assessment of global left ventricular function is the evaluation of LV wall motion. The following is an overview of how regional wall motion abnormalities (RWMA) are evaluated by TEE. The ability to precisely localize LV regional wall motion abnormalities is essential in guiding clinical decision-making and the impact of therapy especially in coronary artery bypass graft (CABG) surgery. Accurate evaluation and documentation of RWMA are key factors for the communication between the echocardiographer and the surgeon. Therefore, in 1989, the American Society of Echocardiography adopted a 16-segment model to form a comprehensive evaluation and documentation of left ventricular performance with regard to regional wall motion (Schiller, 1989).

The system is based on the division of the left ventricle into the apical, mid, and basal zones with the basal and mid zones containing six segments each. The apical zone has only four segments because of its smaller area (Figure 2.17).



Basal Segments	Mid Segments	Apical Segments
1= Basal Anteroseptal	7= Mid Anteroseptal	13= Apical Anterior
2= Basal Anterior	8= Mid Anterior	14= Apical Lateral
3= Basal Lateral	9= Mid Lateral	15= Apical Inferior
4= Basal Posterior	10= Mid Posterior	16= Apical Septal
5= Basal Inferior	11= Mid Inferior	
6= Basal Septal	12= Mid Septal	

Figure 2.17. 16-segment model of the left ventricle. From Shanewise JS, *AnesthAnalag*, 1999, p. 875, with permission.

In order to fully assess all 16 segments, five imaging planes must be utilized: the midesophageal (ME) four-chamber, two-chamber, and long-axis views as well as the transgastric (TG) mid and basal views. Although laborious, it is essential in clinical situation where precise interrogation is critical (CABG surgery). The 16-segment system was also adopted because it provides an accurate representation of the coronary artery perfusion zones. The TG short-axis view is commonly used to evaluate regional wall motion because, besides being the easiest to continually assess intracavity area and volume, it displays all three of the LV myocardial territories that are supplied by all three main coronary arteries (Figure 2.18).

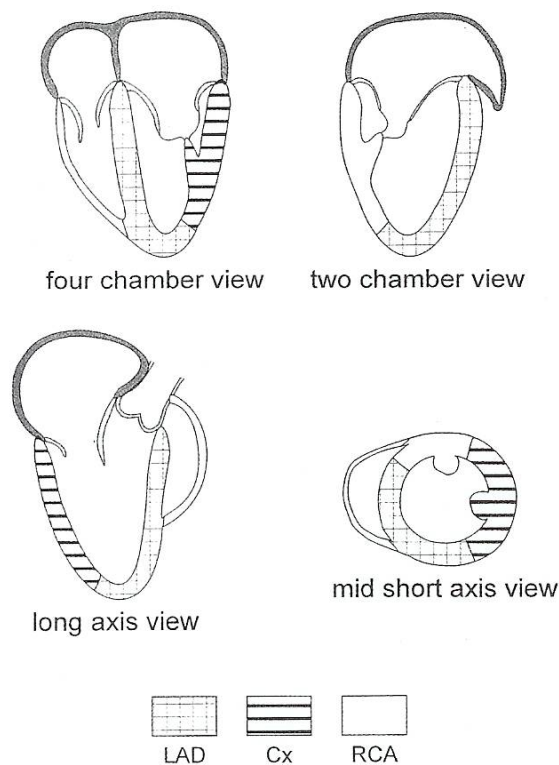


Figure 2.18. Regions of myocardial perfusion by each of the major coronary arteries of the left ventricle. LAD: left anterior descending; Cx: circumflex; RCA: right coronary artery. From Shanewise JS, *Journal of the American Society of Echocardiography*, 1999, p. 890.

Left ventricular wall motion abnormalities are manifested with TEE examination by decreased inward motion called radial shortening and by decreased myocardial wall thickening. Currently in the perioperative setting, a qualitative approach to the recognition of ischemic RWMA is practiced, although semi-quantitative assessment can be accomplished using m-mode (Figure 2.19 and 2.20).

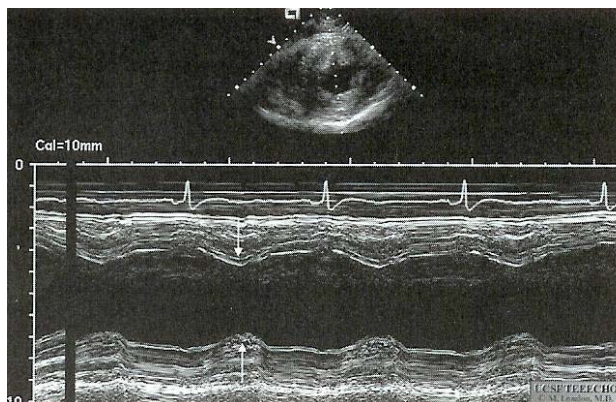


Figure 2.19. Normal wall motion by M-mode (motion mode). Inferior (top arrow) and anterior (bottom arrow) myocardial wall motion and thickness is shown. Top inset provides the TG SAX view from which the m-mode was referenced (dotted line). When coupled with ECG, m-mode can provide information regarding the timing of wall motion. Systole begins with QRS complex and concludes at the end of the T wave (arrows show systolic movement). From London MJ, Chapter 4: Diagnosing of Myocardial Ischemia, In: Perrino and Reeves, *A Practical Approach to Transesophageal Echocardiography*, 2003, p. 58, with permission.

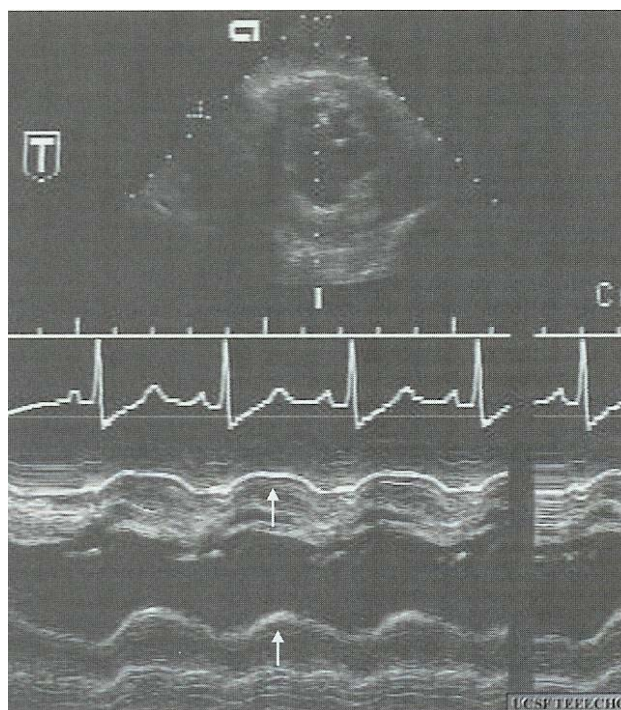


Figure 2.20. Arrows identify regional wall motion abnormality (RWMA) by m-mode as dyskinesia (outward motion of inferior wall shown in upper arrow) during systole in a patient with chronic inferior myocardial wall infarct. Thickening of the inferior wall is also shown in both the m-mode and TG SAX views. From London MJ, Chapter 4: Diagnosing of Myocardial Ischemia, In: Perrino and Reeves, *A Practical Approach to Transesophageal Echocardiography*, 2003, p. 58, with permission.

Early work by Smith and colleagues at UCSF established a regional wall motion scoring system that is still in clinical use today and is shown below in table 2.1 (Smith et al., 1985).

Wall Motion	Radial Motion	Myocardial Thickening
Normal Motion	>30%	30%-50%
Mild Hypokinesis	10%-30%	30%-50%
Severe Hypokinesis	0%-10%	<30%
Akinesis	0%	0%
Dyskinesis	Outward Bulging	Systolic Thinning

Table 2.1. Scoring of LV wall motion.

In this study, 50 patients undergoing cardiac surgery were monitored for ischemic changes with five-lead ECG to show S-T changes and regional wall motion with two-dimensional TEE in the TG short-axis view. Ischemia by RWMA was defined by diminished or absent inward endocardial motion and by impaired systolic myocardial thickening. Twenty-four of the 50 patients showed new RWMA compared to only 6 of the 50 showing S-T wave changes. All of those with S-T segment changes suggestive of ischemia also had RWMA. Three of the 50 patients suffered a myocardial infarction, all of who had RWMA, but only one had ECG changes. Following this work, Leung and co-workers, also from UCSF, assessed the prognostic significance of RWMA with TEE compared to ECG, blood pressure, and pulmonary artery pressure in 50 prospective CABG patients (Leung et al., 1989). Post-bypass ischemia (RWMA) observed with TEE was predictive of adverse outcomes (postoperative myocardial infarction, ventricular failure, and death) in 6 of 18 patients as compared with 0 of 32 without TEE ischemia ($P=0.001$). In addition, 73% of the TEE ischemic episodes occurred without any acute changes in ECG, blood pressure or pulmonary artery pressure.

Presently there is some discussion that although RWMA is a sensitive indicator of ischemic changes, early TEE literature may have mistakenly thought that newly diagnosed RWMA identified all patients developing perioperative myocardial ischemia (London, 2003). In his chapter on diagnosing myocardial ischemia, London states that

current research in complex manifestations of myocardial ischemia such as myocardial “stunning” and “hibernation” may complicate the ability to immediately assess the heart’s viability. To identify these newer complex characteristics of myocardial ischemia, dobutamine stress testing is being emphasized as a preoperative test in non-cardiac surgery for the purpose of risk stratification (London, 2003). A chronic transmural infarction will not respond by increased wall thickening in the affected area when dobutamine is administered. Improvement in wall function is observed, however, in the akinetic segment of a stunned myocardium when low-dose dobutamine is given indicating viable myocardium with inherent contractile reserve. A biphasic response is seen in a hibernating myocardium in which low doses of dobutamine show an improvement in wall motion followed by deterioration in function at higher doses. London also goes on to say that monitoring the heart in non-cardiac surgery for the sole purpose of assessing regional wall motion to detect ischemia may be on the decline. The use of TEE in cardiac surgery for monitoring ischemic changes, however, continues to increase and is considered to be the standard of care, especially in the newer surgical procedure of off-pump coronary artery bypass graft surgery, or OPCAB.

The evaluation of regional wall motion is part of any comprehensive assessment of the heart when the TEE probe is initially inserted. If the patient is at risk for ischemia or has a known segment of wall motion abnormality diagnosed by preoperative echocardiography, it is prudent to make a baseline interrogation of this region shortly after induction of anesthesia and save it on either videotape or a digitalized system so that the image can be retrieved intraoperatively and compared alongside updated images for signs of ischemic changes. Even while managing a critically ill patient, the practitioner

must remain vigilant to changes in myocardial perfusion. This is analogous to remaining vigilant to intraoperative ECG changes in virtually every surgical patient.

Review of the Literature

Perioperative Assessment of Critically Ill Patients with Transesophageal Echocardiography

The evaluation of hypotension in the critically injured trauma patient requires rapid assessment as to its etiology. The TEE probe can be inserted into the esophagus quickly without the need for intravascular access, which is often difficult to attain in the rapid resuscitative tempo of the operating room. The surgical skin prep and trauma surgical draping often precludes internal jugular or subclavian access for invasive monitor placement. Within minutes an assessment of hypotension can be accomplished and the etiology confirmed as either a “pump” dysfunction (aortic injury/cardiac failure) or hypovolemia. Although methods are available for the evaluation of acute onset of hypotension, there is little information in the literature regarding the capability of TEE to quantify intraoperative blood loss. A literature review of the substantive articles retrieved from an in-depth literature search is reviewed in this section.

A search of “transesophageal echocardiography” on PubMed in 2006 resulted in over 11,421 articles located. When “transesophageal echocardiography, intraoperative” was searched on PubMed, well over 1,736 articles was discovered. Likewise, a search of “transesophageal echocardiography, intensive care unit” revealed nearly 300 articles. A significant amount of what this author refers to as the foundational literature in the development of perioperative transesophageal echocardiography has come from both the ICU and OR. The work done by these authors has been influential in advancing TEE in both of these environments. After cross-referencing a number of these articles, it was

discovered that several significant ones were identified in many of the papers read. These articles form the basis of this literature review.

Qualitative estimations are often used to rapidly assess intraoperative volume status. This is especially true with the hypotensive patient in the operating room (OR) or intensive care unit (ICU). This form of assessment requires no special techniques other than experience and a trained eye. Hong described a technique for qualitatively assessing hypotension. The practitioner examines the left ventricle in the trans-gastric short-axis view in systole and diastole and observes for the development of end-systolic cavity obliteration or “kissing papillary muscles” (Figure 2.21), which is considered to be a sign of reduced end-diastolic area (Hong, 1992).

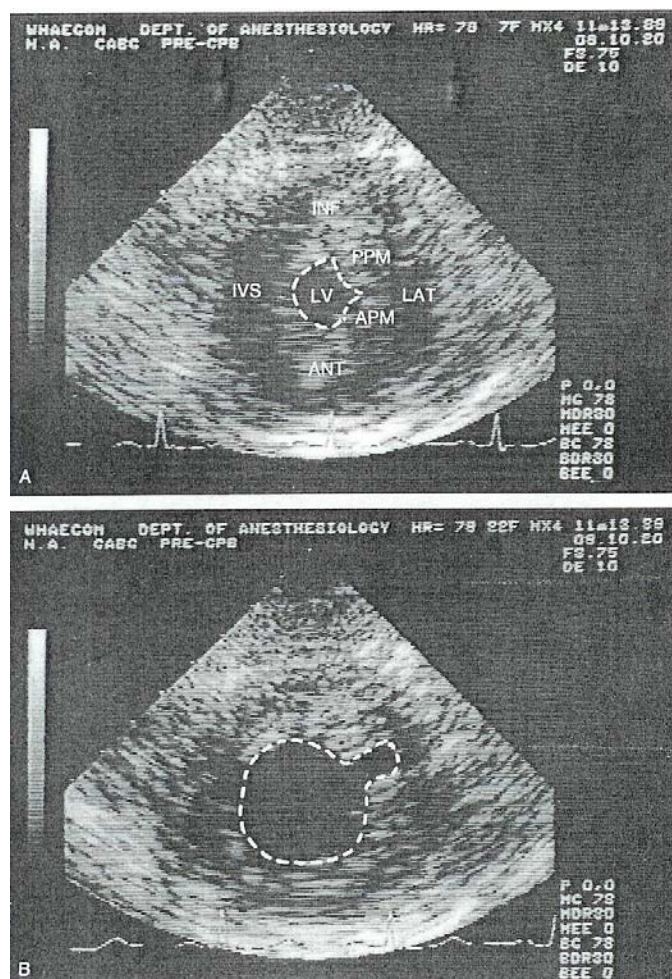


Figure 2.21. A two-dimensional TEE of left ventricle in the transgastric short axis view at the level of the papillary muscles. Image A shows a qualitative assessment of hypovolemia based on the “kissing papillary muscles” as seen on the end-systolic area image. Image B is the left ventricle in diastole. INF: inferior, ANT: anterior, IVS: Intraventricular septum, LV: left ventricle, PPM: Posterior papillary muscle, APM: Anterior papillary muscle. From: Hong and Oka, Chapter 13: Hypotension, In: Oka and Goldiner, *Transesophageal Echocardiography*, 1995, p. 268.

In an attempt to directly study LV end-systolic cavity obliteration and its relation with end diastolic area as an indication of hypovolemia, Leung examined 139 patients undergoing CABG surgery at UCSF/Mount Zion Medical Center (Leung, 1994). A quantitative assessment of EDA, ESA, and FAC dimensions was performed. Thirty-nine of the 139 patients experienced LV cavity obliteration with significant decreases in both ESA ($7.29 \pm 2.56 \text{ cm}^2$ to $4.0 \pm 1.46 \text{ cm}^2$, $p = 0.0001$) and EDA (18.18 ± 4.36 to $12.92 \pm 3.74 \text{ cm}^2$, $p = 0.0001$) with an increase in FAC (0.609 ± 0.095 to 0.692 ± 0.083 , $p =$

0.0001), suggestive of hypovolemia. Interestingly, during these episodes of end-systolic cavity obliteration, no changes in hemodynamic measurements of HR, blood pressure or pulmonary artery pressure were noted. The author concluded that although the sensitivity is high for decreases in ESA to predict decreases in EDA (100%), the specificity as to the cause of the change is low (25%-38%) when a decrease of 10%-30% in EDA is used (researcher's cutoff). Leung goes on to say that low specificity is due to the fact that high incidences of false-positives suggest a number of the decreases in ESA are not always a result of a decreased EDA. Caution must be taken when qualitatively using end-systolic cavity obliteration for assessing intraoperative hypovolemia since increased contractility (use of intraoperative vasoactive medications) or decreased afterload (decreased systemic vascular resistance from sepsis or neurological injury) could also affect left ventricular cavity size (Leung, 1994).

Confident that during significant acute hypotension, qualitative TEE examination and estimates of ventricular filling and function are important in guiding fluid replacement and pharmacologic therapy, Cahalan has developed a TEE examination modified from the original comprehensive 20 TEE views previously described (Shanewise et al., 1999). This 12-view examination is shown in Figure 2.22 below.

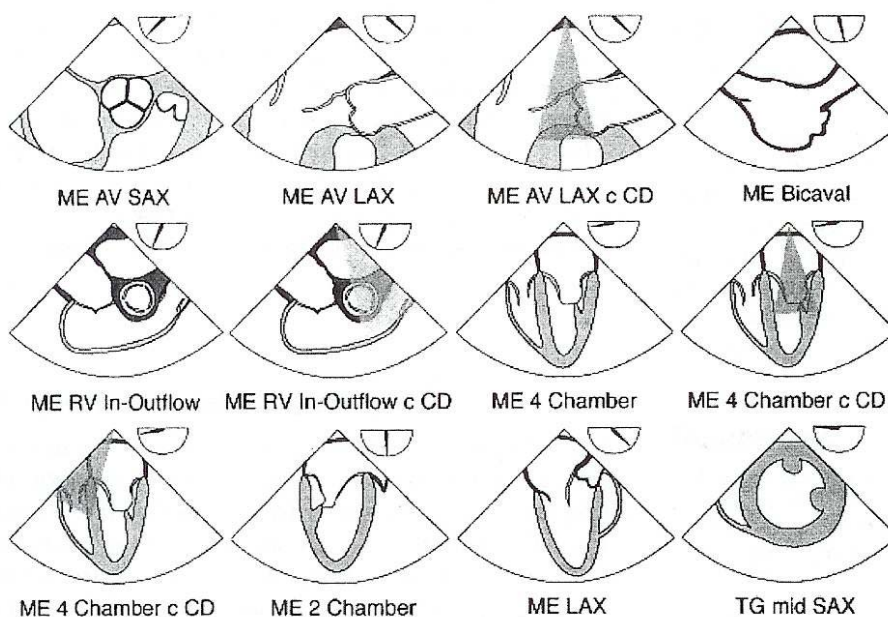


Figure 2.22. The eight basic cross-sections along with the four cross-sections that utilize color Doppler (c CD). From: Cahalan MK, Anesthesia and Analgesia, 2004, p. 12, with permission.

In what he calls “Rescue Transesophageal Echocardiography,” Cahalan describes his technique of limited movement of the TEE probe to acquire the necessary images to perform the examination (Cahalan, 2004). The diagnostic goal of rescue TEE is to rapidly detect “markedly abnormal ventricular filling or function, extensive myocardial ischemia or infarction, large air embolism, severe valvular dysfunction, large cardiac masses and thrombi, large pericardial effusions, and major lesions of the great vessels” (p. 11). The author predicts that, with experience, this technique can be accomplished in 2-3 minutes where the comprehensive examination can take up to 15 minutes to complete.

Cahalan often uses a table to illustrate qualitative measurements of LV end-diastolic area as a reference to diagnose hypovolemia. This author has attended two TEE training courses at which Dr. Cahalan has presented this material. Below is the table he often uses.

LVEDA	EFA	Diagnosis
↓	↑	Hypovolemia
↑	↓	Myocardial depression or ischemia
↔	↑	Low systemic resistance

Table 2.2. Evaluation of acute hypotension with TEE probe in the LV SAX view. LVEDA: Left ventricular end-diastolic area, EFA: Ejection fraction area.

When the LVEDA is decreased, an increase in the EFA, also known as FAC, is observed.

This coincides with what Leung reported in her work (Leung, 1994). In hypovolemic states, the heart attempts to compensate for a decreased LVEDA by increasing cardiac output (Boulpaep, 2003a; Mohrman, 2003). Likewise, when there is a lowered systemic vascular resistance, as encountered in septic shock, an increase in the EFA (FAC) is observed, however, there may not be any change in the EDA since there is no significant volume loss. Finally, the table indicates that in myocardial depression or ischemia, an increase in EDA will be noted, however, there is a decrease in the EFA (FAC) due to the inability of the heart to effectively contract (Boulpaep, 2003a; Mohrman, 2003).

Although a qualitative approach to establishing the etiology of hypotension is of vital importance in the ICU and OR, quantitative assessment is essential for establishing a method as a valid form of measurement. The following articles are significant contributions to this end. They are separated by whether the research was performed in the ICU or the OR. Those that directly influence this author's research plan are presented in Table 4 at the end of the chapter.

As TEE moved into the perioperative area, the feasibility, safety, and its impact on critically ill patients was determined. Early work by Khoury and colleagues at Baylor University compared the newer technique of TEE to the established method of transthoracic echocardiography (TTE) when TTE was inadequate or its results were inconclusive (Khoury, 1994). The general indication for performing TEE in the 77

critically ill patients was most commonly for hemodynamic instability (41%).

Echocardiography was responsible for changes in management in 46 of the 77 patients studied (60%). In thirty-seven of those patients (48%), the findings from TEE assessment led to changes in medical management in 19% and surgical intervention in 29%. The authors concluded that TEE was a safe and powerful diagnostic tool in guiding patient management in the ICU.

Hwang and associates reported similar results from the National Taiwan University Hospital in the Republic of China in their study of both TEE and TTE in 80 patients (Hwang et al., 1993). Forty-eight patients were evaluated in the ICU while, interestingly, 32 were assessed in the emergency department (ED). Transesophageal echocardiography was able to provide crucial information that was unobtainable with TTE in 39 of the 78 patients (50%, $p < 0.005$). Hemodynamic instability (22 patients) was the second most frequent indication for TEE assessment preceded by suspected aortic dissection (34) patients. Emergent surgical intervention was indicated in 14 patients (18%), all of them being confirmed in the OR. The authors concluded that TEE provided a safe, valuable tool for the assessment of critically ill patients.

In their study of 61 patients with >60 minutes of unexplained hypotension in the ICU, Heidenreich and fellow investigators at UCSF compared image acquisition of TEE with TTE (Heidenreich et al., 1995). With endpoints of death or discharge from the ICU, these investigators reported improved outcome with echocardiography in 81% of the patients with non-ventricular disease compared to 41% with ventricular pathology. An improvement of 44% was seen in patients diagnosed with hypovolemia and or decreased systemic vascular resistance. Inadequate image acquisition was, however, experienced

more with TTE (29/45, 64%) compared with TEE (2/61, 3%, $P < 0.001$). With new clinically significant diagnoses discovered in 17 patients (28%) of which 12 required surgery (20%), these investigators concluded that TEE provided clinically important assessments that significantly contribute to the diagnosis and management of critically ill patient. Studies comparing image acquisition between TTE and TEE were also reported by Oh (n=51 patients), Pearson (n=61 patients), Stoddard (n=81 patients), and Vignon (n=111 patients) who came to similar conclusions. All the investigators reported approximately 25% of the patients having their ICU clinical management altered by echocardiographic findings (Oh et al., 1990; Pearson, Castello, & Labovitz, 1990; Stoddard, Liddell, Vogel, Longaker, & Dawkins, 1992; Vignon et al., 1994).

The difficulties encountered with TTE are well established in most echocardiography and cardiac anesthesia textbooks and are accepted as a limitation to its utility in critically ill patients (Otto, 2000; Troianos, 2002). Cook and colleagues at Ohio State University published their findings that examined what factors were associated with the failure of TTE to acquire the necessary images and the cost-effectiveness of TTE in this patient population (Cook, Praba, Beery, & Martin, 2002). Their retrospective review of critically ill surgical ICU patients discovered three factors that made TTE unable to obtain adequate images: an increase in admission weight of $>10\%$ (usually from third spaced fluid causing edema formation), positive end-expiratory pressure of >15 cmH₂O, and chest tubes *in situ*. They also reported that, in patients possessing any of these factors, TTE was not cost-effective and that TEE was a better alternative.

In addition to determining the feasibility of TEE in perioperative patient management, other researchers examined the ability of TEE to quantify cardiac volume.

Early studies were aimed at seeking validation of TEE to determine LV preload while others examined the optimum view to assess this measurement. Clements and colleagues at Duke University published an early paper that compared TEE to simultaneous radionuclide angiography (RNA) (Clements, Harpole, Quill, Jones, & McCann, 1990). Adequate images were obtained in 12 of 14 patients undergoing abdominal aortic aneurysm resection. The LV cavity was measured by TEE in the trans-gastric short-axis view at the level of the mid-papillary muscles. End-systolic and end-diastolic areas (ESA, EDA) were compared with end-systolic and end-diastolic volumes (ESV, EDV) measured by RNA. Area ejection fraction (AEF), which is commonly referred to as fractional area change (FAC), had strong correlation with ejection fraction ($r = 0.96$). There was equally strong correlation between EDA and EDV ($r = 0.86$) and ESA and ESV ($r = 0.92$).

Urbanowicz and associates at UCSF reported similar results with their study comparing EFA (in the same probe position) to radionuclide scintigraphy (the use of a radioactive substance injected intravenously to outline and examine organs or tissues) (Urbanowicz, 1990). Good correlation was reported between EFA (FAC) derived from TEE and EF from scintigraphy ($r = 0.82$) in 10 postoperative CABG surgical patients with the authors concluding that TEE derived EFA provided a reasonable estimate of ejection fraction.

Automated border detection (ABD) has also been evaluated to determine if this technique provides similar results as those found with EDA derived from off-line manual planimetry as reported above. In an elaborate open-chest animal model, Morrissey and colleagues at the Massachusetts General Hospital studied 4 dogs to evaluate true end-

systolic and end-diastolic volume and ejection fraction by ABD, off-line planimetry, and actual blood flow that was controlled through a fully cannulated heart (Morrissey, 1994). Underestimation was found with ABD as previously discussed, however, these researchers reported that both on-line and off-line estimations of ejection fraction correlated well with true EF calculated from the actual ventricular volumes ($r = 0.94$ and $r = 0.96$, respectively).

Radionuclide comparisons with ABD have also been assessed in human investigations. Liu and fellow researchers in Paris found good correlation between EFA (FAC) estimated by ABD and ejection fraction by radionuclide scintigraphy ($r = 0.85$) in 10 critically ill patients, concluding that ABD FAC determined by ABD may be used to quantify LV function in the ICU (Liu, 1996). In an interesting study of 20 healthy male volunteers, Grandi and colleagues in Italy examined the sensitivity of TEE using ABD to small changes in preload (Grandi et al., 1997). By using position changes and sequentially controlling blood with tourniquets on all four extremities, these researchers were able to demonstrate changes in end-systolic and end-diastolic volumes while FAC remained constant. This study is significant in that it provides data that TEE can detect small changes in preload in the healthy heart. Most of the clinical research described in the literature is performed on cardiac patients who have pre-existing cardiac pathology. The work from these authors was instrumental in establishing TEE in the ICU. Review articles in critical care medicine also recognized TEE as both a valid and meaningful method for the assessment and management of the critically ill ICU patient (Heidenreich, 2000; Skiles, 2000; Troianos, 1996).

Kolev and colleagues published a multicenter study of seven European countries to evaluate the influence of intraoperative TEE use in cardiac and non-cardiac surgical procedures (Kolev et al., 1998). Of the 224 patients studied (2232 clinical interventions), the most frequently observed TEE intervention was for guiding fluid boluses (45%) and, overall, TEE was considered most important factor in patient management in 560 interventions (25%). These investigators reported that TEE often guided clinical decision-making in category II indications for TEE use (Thys, 1996) but had its most significant impact on intraoperative management of Category I indications (See Appendix 2). Below (Figure 2.23) is a graph showing clinical interventions in which TEE was supportive in clinical intraoperative decision-making compared to ECG, arterial pressure, and PAC.

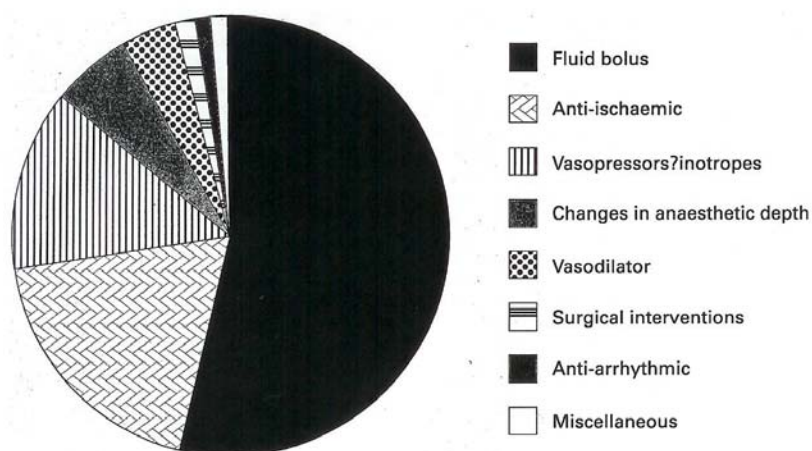


Figure 2.23. Use of TEE in guiding intraoperative decision-making. Read clockwise from 1200. *Anaesthesia*, 1998, with permission.

The two most common reasons for supportive TEE guided management were for the assessment of fluid boluses and the evaluation of ischemia with anti-ischemic therapy.

In a study by Colreavy and fellow investigators in Australia, TEE was most often used in evaluating and guiding clinical management of the patient with unexplained hypotension (Colreavy, 2002). Of the 308 studies performed on 255 critically ill patients,

TEE was able to identify the cause of hemodynamic instability in 67% of the cases with improvement in 31%. These investigators continue to advance the use of TEE in critically ill patients who present with hemodynamic instability.

Suriani and colleagues at Mount Sinai Medical Center in New York retrospectively examined TEE video recording and medical records of 123 non-cardiac surgical patients (Suriani, Neustein, Shore-Lesserson, & Konstadt, 1998). Of the 123, 55 patients were examined at the request of another attending anesthesiologist as a consultative procedure by an anesthesiologist certified in TEE. The significance in reporting this work is that it exemplifies the importance that TEE provides for the rapid intraoperative evaluation of patients with hemodynamic instability. The main reason for its use in this study was for the appraisal of LV function. Surgical demographics revealed that general surgery patients were the most common patients evaluated and major abdominal surgeries were the most common surgical procedure being performed when TEE was called in for evaluation. Suriani's work, along with studies by Kolev and Colreavy, establishes the need for rapid intraoperative TEE availability for the evaluation of patients exhibiting signs of hemodynamic instability.

Because of the professional relationship between cardiologists and cardiac anesthesiologists in the management of cardiac surgical patients, their combined work advanced the evolution of TEE in the intraoperative area. Many of the studies discussed are collaborative efforts between these two specialties (e.g.: Cahalan and Schiller at UCSF). As the interest for TEE guided assessment has moved out of the cardiac surgical suites and into non-cardiac surgical procedures, volume estimation has been a topic of study by various investigators. A significant concern is the ability to assess intraoperative

volume status with TEE without having to continually manipulate the probe into different views. This probe manipulation can be time consuming and take away from the anesthetic management of the patient. This is one criticism against the use of TEE. For this reason, it is now generally considered that the preferred intraoperative imaging view for the evaluation of systolic function is the transgastric short-axis (TG SAX) view at the level of the mid-papillary muscles (Walton, 2003). Because the heart's predominant contractile force is along its short axis, compared to the limited contraction of the apex towards the base, the TG SAX view provides a real-time image for the rapid continuous assessment of global LV function and volume status. As previously described, this view also affords an assessment of regional wall motion along with the myocardial regions perfused by the three major coronary arteries (left anterior descending, circumflex, and right coronary artery).

The use of LV end-diastolic area from the TG SAX view as a surrogate for assessing preload is considered a standard practice and is described in most TEE textbooks (Otto, 2000; Troianos, 2002). Review articles by Hanowell and colleagues, Troianos and Porembka, Skiles and Griffin, Walton and associates, and Worab and Huemer all identify the TG SAX view as the most commonly used position of the TEE probe for on-going volume assessment and LV function (Hanowell, 1998; Skiles, 2000; Troianos, 1996; Walton, 2003; Wolrab et al., 1997).

The following literature reviewed utilizes the measure of preload (EDA) to evaluate hemodynamic changes occurring from the systematic removal of blood and are summarized in Table 2.3.

In a study by Cheung and colleagues at the University of Pennsylvania, thirty-five cardiac patients undergoing general anesthesia for coronary artery bypass grafting (CABG) were stratified into two groups: those with normal left ventricular function (group 1, n = 17) and those with abnormal left ventricular function (group 2, n = 13); five patients did not undergo hypovolemia and acted as control to test for time-dependent changes (group 3) (Cheung et al., 1994). The purpose of this study was to determine what effect graded hypovolemia had on TEE measures of left ventricular function. Table 3 reflects the measurements taken during the graded hypovolemia, which required a 2.5% graded removal of blood in six aliquots to a maximum of 15% of the patient's calculated total blood volume. Left ventricular EDA had a mean change of 0.3 cm² for every 1.0% of blood removed in both group 1 and 2. The study demonstrated that TEE is sensitive enough to detect and monitor hemodynamic changes resulting from graded blood removal in cardiac patients undergoing general anesthesia for CABG surgery. These researchers also demonstrated that changes in EDA (preload) produced by graded blood removal were not statistically different between patients with normal (Group 1) and abnormal (Group 2) wall motion.

At nearly the same time, Reich and colleagues at Mount Sinai Medical Center in New York, tested whether TEE could detect changes in cardiac filling using graded blood removal in pediatric cardiac patients (Reich et al., 1993). In this observational study, eleven patients who underwent repair of their congenital cardiac lesions were subjected to blood withdrawal from an indwelling CVP catheter to produce a 5mmHg and 10mmHg decrease in the systolic blood pressure after baseline readings of EDA. These data also found that EDA was a "potentially useful indicator of cardiac filling" (p. 10). In this same

work, Reich and his colleagues determined that TEE had a sensitivity of 80% (with a 5mmHg change) and 95% (with a 10mmHg change), respectively and a specificity of 80% in identifying mild reductions in blood volume.

While the TEE literature contains strong supportive data that EDA is an accepted measure of cardiac preload, the work by Cheung and Reich provides the only evidence that EDA can detect real-time blood loss. Both of these authors, however, studied cardiac patients undergoing cardiac surgical procedures and, therefore, the data are relevant to cardiac patients with preexisting cardiac pathology.

Two recent animal studies have also examined TEE in the detection of blood loss on LV preload. Swenson and colleagues at the University of Utah used Automated Boarder Detection (ABD) to investigate if TEE could be used to determine an end-point to volume replacement in a hemorrhagic animal model (Swenson et al., 1996). These researchers did not use TEE to monitor blood loss but rather to establish its capability to guide volume resuscitation. The removal of blood was guided by CVP measurements to achieve a pressure of between 0-5mmHg, which resulted in a blood removal of between 20-35mL/Kg of animal weight. EDA was compared to PAWP to ascertain which measurement could best identify when a maximal cardiac preload was reached based on cardiac output. The investigators explored the Frank-Starling law of cardiac muscle fiber stretch to hypothesize that there would be a point where additional increases in volume (preload) would have minimal effect on output (maximal fiber length had occurred). Only EDA measured by ABD was able to detect maximal volume loading when compared to PAWP, which showed no peak in its pressure measurements of increasing cardiac filling.

In a more recent animal study involving eighteen male pigs undergoing general anesthesia, Dalibon and his colleagues in Paris, France also assessed graded hemorrhage and re-transfusion (Dalibon, Schlumberger, Saada, Fischler, & Riou, 1999). Left ventricular EDA was compared to PCWP and mean arterial pressure (MAP). Interestingly, EDA was more accurate than either PCWP or MAP at assessing graded blood loss, however PCWP was more reliable at detecting a return to pre-hemorrhage baseline. A significant difference between this study and the previous three is that Transthoracic Echocardiography (TTE) was used to measure EDA.

Tousignant and colleagues in Toronto investigated the relationship between LV EDA and stroke volume (SV) in 41 critically ill patients in the ICU (Tousignant, 2000). The investigators examined whether EDA could identify patients who responded to boluses of 500 ml of pentastarch by increasing their SV by 20%. Modest correlation was reported between EDA and SV ($r = 0.60$). EDA was significantly lower ($15.3 \pm 5.4 \text{ cm}^2$) in those who responded to the bolus compared to the non-responders ($20.2 \pm 4.8 \text{ cm}^2$, $p = 0.026$). Interestingly, data from the PAOP showed no correlation with SV ($r = 0.15$), and PAOP rose significantly in both the responders and non-responders alike. Two important points regarding this study must be made. First of all, the authors concluded that planimetric assessment of LV EDA obtained by TEE in the mid-papillary TG SAX view reliably predicts a response to fluid administration. The second point is that this study confirms and cites the earlier work by Cheung et al, and Reich et al regarding EDA as a reliable measure of preload during blood removal. These studies provide a basis for the belief that TEE can reliably estimate LV preload and determine LV volume changes using the TG SAX view in the cardiac surgical patient and animal model.

In addition to the previously discussed work by Cahalan and colleagues, Perrino and investigators at Yale University also studied ABD in 16 patients undergoing non-cardiac surgery and compared their results with manual off-line planimetry (Perrino, Luther, O'Connor, & Cohen, 1995). These researchers reported a high correlation between ABD and manual estimates of LV ESA ($r = 0.93$), EDA ($r = 0.89$), and FAC ($r = 0.90$), an accuracy of 96% in tracking serial changes in LV area measurements and a sensitivity of 83% and specificity of 85% for detecting acute changes in LV area. Although these data are different from those of Cahalan et al (ESA: $r = 0.94$, EDA: $r = 0.98$, FAC: $r = 0.80$), some of the differences may be due to lost data as reported by Cahalan and experience with image acquisition since Cahalan's work was published in 1993 and Perrino's in 1995.

Recently, the additions of color have been attempted in the newer prototypes of ABD technology to enhance motion detection. This technique, called color kinesis, has not yet been made available for routine clinical evaluations (Bednarz, 1998). Echocardiographic contrast has also recently been used experimentally to improve image quality by these same authors (Spencer, 2002). These techniques are not a part of common TEE practice at this time, but illustrate the work being done to improve ABD.

To conclude this section, although TEE may underestimate absolute LV volumes with on-line methods like ABD, during intraoperative fluid assessment and management the changes in LV preload detected with TEE is more important than acquiring absolute volumes. In addition, intraoperative clinical decision-making is more commonly based on a change in hemodynamic trends rather than on an absolute number. Therefore, TEE

continues to play an important part in the assessment of LV function and volume status and will likely expand in its use for guiding intraoperative clinical decision-making.

The combined use of the PAC and TEE is common practice to help define PAC parameters that reflect maximal preload based on the correlation with TEE estimations of EDA. This was confirmed during a personal interview with Dr. Cheung regarding his early work in this area (Cheung, 2004; Cheung et al., 1994). The TEE probe is not usually kept *in situ* for long periods of time so as not to cause soft tissue damage to delicate pharyngeal and gastric mucosal structures. Knowing the PAC data that reflect optimal cardiac filling with the concurrent TEE evidence allows the TEE to be reinserted only if hemodynamic instability reoccurs (Cahalan, 2004; Hanowell, 1998; Tousignant, 2000).

The Application of Three-Dimensional TEE for Left Ventricular Volume Analysis in Clinical Practice

Three-dimensional (3D) echocardiography has recently become available for clinical application. The 3D technology, however, has been available since the early 1980's (Ariet, Geiser, Lupkiewicz, Conetta, & Conti, 1984; Linker, Moritz, & Pearlman, 1986). The limitation to its clinical utility was that computer software technology at that time had not reached a level to accommodate 3D ultrasound technology (Gunasegaran, 2000). Although found to have good correlation by Pai and colleagues when compared to cardiac CT ($r = 0.89$) (Pai et al., 1996), 3D acquisition remained tedious and time-consuming making its clinical utility impractical (Pandian et al., 1994). It was not until after 2000 that 3D software became available for clinical use (von Bardeleben, Kuhl, Mohr-Kahaly, & Franke, 2004). At that time, off-line data processing was still the standard and mainly directed towards 3D analysis of cardiac structures such as the mitral

and aortic valves (Gunasegaran, 2000; Macnab et al., 2004). The off-line use for cardiac volume measurement made 3D impractical in the perioperative setting.

Case reports regarding 3D use and benefits for the structural analysis of cardiac valves have been reported in the literature. Baweja and colleagues at the University of Alabama at Birmingham describe in a case report the capability of 3-D TEE to identify a membranous intraventricular septal aneurysm that caused an obstruction of the right ventricular outflow tract (Baweja et al., 2004). In addition to providing outstanding 3-D structural images of the heart, when combined with color flow Doppler, this new technology has also been reported to produce exceptional regurgitant flow images (Figure 2.24).

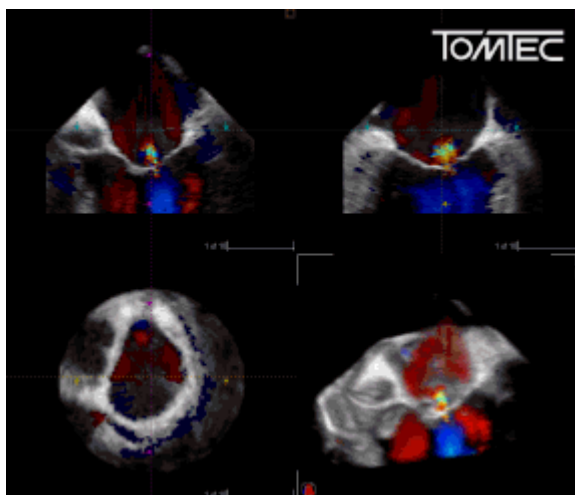


Figure 2.24. Three-dimensional image of mitral regurgitation with 3D imaging and color Doppler. From: TomTec Imaging Systems, Unterschleissheim, Germany, www.tomtec.de

A case report by Sugeng and associates at the University of Chicago described color flow Doppler with 3-D TEE in identifying and analyzing a mitral valve regurgitation (Sugeng et al., 2003). Macnab and colleagues in the United Kingdom considered three-dimensional TEE to be superior to conventional two-dimensional imagery for diagnosing

regurgitant mitral valve morphology in 75 patients diagnosed with mitral valve disease (Macnab et al., 2004).

Three-dimensional TEE may also be valuable in assessing volume changes in the left ventricle. In early work done by Yagi and colleagues and Hozumi and associates, 3-D TEE correlated well with left ventriculography in estimating left ventricular volume ($r = 0.97$) and ejection fraction ($r = 0.95$) (Hozumi et al., 1996; Yagi et al., 1996). In an *in vitro* model Kuhl and colleagues reported excellent correlation between 3-D TEE and angiography in estimations of ejection fraction (EF) ($r = 0.998$), end-systolic volume (ESV) ($r = 0.996$), and end-diastolic volume (EDV) ($r = 0.998$) (Kuhl et al., 1998). To date, there have been no studies reported in the literature comparing 2-D TEE measurements of ESA, EDA, and FAC obtained by off-line planimetry with the newer 3-D measurements of ESV, EDV, and EF.

With the development of more powerful and faster computer processing capabilities, real-time 3D imaging has been introduced into clinical practice in the last year. Still in its infancy, real-time 3D analysis is available with only transthoracic echocardiography (TTE) at this time. Therefore, the literature generated in the last year has been unable to provide any data concerning real-time 3D measurements with the transesophageal approach, which is thought to provide better image resolution (Gunasegaran, 2000). At this time 3D TEE structural and volume analysis continues to be completed off-line.

An updated review of the literature for the last two years discovered six articles with respect to real-time 3D echocardiography. Interestingly, four of the papers that were published in three different journals are from the same group of authors based at the

University of Chicago. Upon further reading and the networking that has occurred as a result of this author's research project, it appears that the University of Chicago was the testing ground for the new real-time 3D technology. This would make sense when put into context as the University of Chicago was a major center in the development of transesophageal echocardiography, the others being Albert Einstein University in New York and the University of California in San Francisco. In addition, the authors of a study in Madrid, Spain also collaborated with the University of Chicago group in the evaluation of the new 3D technology.

In 2005, investigators in Madrid, Spain compared LV volume and ejection fraction (EF) of 35 patients ages 31 to 87 years with cardiomyopathy measured with real-time 2D TTE, 3D TTE, and cardiac magnetic resonance (CMR) imaging (Gutierrez-Chico et al., 2005). They reported moderate to strong correlation between 2D TTE, 3D TTE, with CMR imaging for EF ($r = 0.92, 0.98$, respectively), EDV ($r = 0.77, 0.99$, respectively), and ESV ($r = 0.86, 0.99$, respectively). The values given are those obtained with the most plane cuts used for reconstruction of the 3D LV image (8 planes). The authors discovered that the accuracy of the 3D LV volume correlated with the number of cut planes used to reconstruct the 3D LV image. They advised 4 cut planes for EDV <150 ml and 8 cut planes for EDV >150 ml to diminish any underestimation of LV volume. The authors also reported that 2D TTE systematically underestimated LV volumes in patients with an EF <50% and cardiomyopathy. This study offers information on the number of TTE cut planes needed for optimum LV chamber reconstruction in patients with cardiomyopathy and supports the literature of moderate to strong correlation of 3D LV volume measurement with the transthoracic echocardiographic approach.

Investigators from the University of Chicago reported two studies exploring real-time 3D TTE for rapid quantification of LV volume and global and regional function. Jacobs and colleagues compared real-time 2D TTE images with real-time 3D TTE images of LV volume and EF. In addition, the group compared the 3D images with CMR imaging (Jacobs, 2006). Fifty patients age 58 ± 19 years with CAD, cardiomyopathy, and valvular disease were evaluated with 2D TTE, 3D TTE, and CMR imaging to compare LV volume. The authors reported the strongest correlation between measurements of real-time 3D and CMR imaging for EDV, ESV, and EF ($r = 0.96, 0.97,$ and $0.93,$ respectively). A moderate to strong correlation was reported between 2D TTE and CMR imaging for EDV, ESV, and EF ($r = 0.89, 0.92,$ and 0.86). These data suggest that real-time 3D by TTE can be used clinically for accurate estimations of EDV, ESV, and EF in a reasonably short time of 2 minutes or less.

In August of 2005, Corsi and investigators from the University of Chicago reported their findings on real-time 3D TTE for volumetric quantification of global and regional LV function in 30 patients age 58 ± 19 years with similar presenting diagnoses of CAD, cardiomyopathy, and valvular disease (Corsi et al., 2005). Three protocols were developed. Protocol 1 examined 16 patients with normal wall motion and reported strong correlation between 3D TTE and CMR imaging for EDV, ESV, and EF ($r = 0.99, 0.99,$ and $0.98,$ respectively). Protocol 2 compared 9 patients with dilated cardiomyopathy to 9 patients with normal LV wall motion. As expected, regional wall motion evaluated by LV volume-time curves was significantly different between the two groups ($p < .05$). Protocol 3 compared 3D TTE with visual interpretation by an expert of LV wall motion; there was a reported 86% agreement (170 of 198 segments). Misclassification of wall

motion as abnormal was 9.1% (18 of 198 segments), and 5.1% (10 of 198 segments) were misclassified as normal. These data confirm that real-time 3D TTE is both rapid and clinically feasible.

In 2006, three publications examined real-time 3D transthoracic echocardiography for the evaluation of LV volume and function. Sugeng and colleagues from the University of Chicago examined 31 patients (60 ± 15 years) who were scheduled for CMR imaging (considered the gold standard) and who underwent same day 3D TTE and cardiac CT (CCT) (Sugeng et al., 2006). Linear regression analysis reported a high correlation between all three modalities for LV volume ($r^2 = 0.93-0.96$); CCT-derived EF was lower ($r^2 = 0.85$). CCT also overestimated EDV and ESV (26 ml and 19 ml, respectively) and underestimated EF slightly (-2.6%). Real-time 3D TTE slightly underestimated EDV and ESV (-5 ml and -6 ml, respectively). Their conclusions were that CCT provided highly reproducible LV volume measurements, which may be significantly larger than CMR. In addition, real-time 3D measurements compared more favorably with CMR. These data continue to validate real-time 3D TTE when compared to the gold standard of CMR imaging.

Nesser and colleagues of the University of Chicago also studied volumetric quantification of 16 regional segments for LV function in 31 patients age 60 ± 15 years with normal function ($n = 15$) and cardiomyopathy ($n = 16$) (Nesser, 2006). This study, similar to the studies by Corsi et al, 2005, and Jacobs et al, 2006, compared expert interpretation of regional wall motion and volumes with real-time 3D TTE and CMR imaging. Regional LV volumes correlated well with CMR for RESV, REDV, and REF ($r = 0.82, 0.85, \text{ and } 0.71$, respectively). Sensitivity, specificity, and accuracy for real-time

3D and CMR compared to expert interpretation reported good agreement (sensitivity: 0.84 and 0.85; specificity: 0.78 and 0.81, accuracy: 0.84 and 0.84, respectively). Again, the investigators provided data to support the accuracy of 3D TTE quantification of regional LV volume analysis and function when compared to CMR imaging.

A publication from Jenkins and investigators in Brisbane, Australia also examined the feasibility of on-line 3D TTE and compared it to 2D TTE, off-line 3D TTE and CMR imaging in 110 patients age 63 ± 10 years (Jenkins, Chan, Hanekom, & Marwick, 2006). As also previously reported by Sugeng et al, 2006, underestimation of LV volumes were noted in all methods, but EF volumes were similar. The best correlation was observed between CMR imaging and off-line 3D TTE (EDV: $r = .86$; ESV: $r = .91$; EF $r = .81$; $p < .01$) when compared to on-line 3D TTE (EDV: $r = .78$; ESV: $r = .86$; EF: $r = .64$; $p < .01$). The lowest correlation was between CMR imaging and 2D TTE (EDV: $r = .71$; ESV: $r = .80$; EF: $r = .60$; $p < .01$). The significance of these data underscores the levels of accuracy between the modalities with off-line 3D evaluation the most accurate followed by 3D on-line and 2D on-line assessments, respectively. It also illustrates that on-line 3D volume assessment is feasible and both methods of 3D analysis are more accurate compared to 2D TTE. Again, it is emphasized that these data are with 3D transthoracic echocardiography because no data for 3D transesophageal echocardiography is available for review since the software for the transesophageal approach has been commercially available since October of 2005.

Transesophageal Echocardiography for Guiding Volume Assessment and Replacement in Trauma

A review of the literature supports that TEE is useful in the evaluation and monitoring of cardiac function and, more specifically, left ventricular preload as an

indication of volume status in the critical care and trauma patient population. End-diastolic area is a sensitive measure of preload and, when combined with ESA, can provide information regarding cardiac output in the form of fractional area change (FAC). Data from previous studies suggest that TEE can effectively monitor blood loss, however, early work has been in the cardiac patient undergoing cardiac surgical procedures. Both animal and human studies provide limited information and support but suggest that ABD may be effective in monitoring real-time volume status and determining an end-point to volume replacement. The concerns for using ABD are that it requires quality images throughout the cardiac cycles, image acquisition is user-dependent, and FAC may be underestimated. Off-line techniques may be more accurate, but are time consuming, do not provide real-time information, and take away from the anesthetic management of the patient. Technological advancements in TEE software and design may provide enhanced image quality in newer models that are becoming available.

Evaluating TEE for Volume Assessment During Acute Normovolemic Hemodilution

Before TEE can be utilized to evaluate and guide volume resuscitation in the trauma patient, however, it must first be studied in a more controlled environment. An ideal clinical condition is available in the operating room when acute normovolemic hemodilution (ANH) is performed in those patients expected to lose a significant amount of blood. Acute normovolemic hemodilution has been incorporated as a safe and cost-efficient means of controlling the loss of oxygen-carrying red blood cells during surgery and returning the shed blood to the patient after the portion of the surgery that results in large blood loss is complete (Jobes & Gallagher, 1982; Monk & Goodnough, 1998;

Rottman & Ness, 1998; Stehling & Zauder, 1991). Therefore, patients who are undergoing ANH as part of their intraoperative strategy for blood management provide an ideal population to investigate whether TEE can quantify a known volume of blood loss in a human hemorrhagic model. In addition, this model is ideal for evaluating volume replacement of the shed blood after its removal to determine when pre-ANH EDA has been achieved.

Off-line estimations of two-dimensional and Doppler TEE images will be compared. No investigators have compared newer off-line 3D volume TEE measurements of EDV, ESV, and EF with the standard 2D TEE images of EDA, ESA, and FAC. It is the desire of this author to eventually establish on-line real time TEE assessment of LV preload and ejection fraction as a method for guiding volume replacement in the trauma patient.

Summary

This comprehensive literature review identifies TEE as an important monitor for the assessment of both cardiac volume and function. The literature also provides strong evidence that TEE is an important tool in the management of critically ill patients the operating room and intensive care unit. The limitation of 2D TEE for volume assessment is that a two-dimensional image is expected to calculate volume of a three-dimensional chamber. With the recent addition of 3D TEE, the question of whether 3D TEE will make a significant difference in LV volume analysis can now be investigated. In addition, the question of whether 3D TEE will be sensitive to small LV volume changes needs to be explored. This study will examine these questions in a unique human hemorrhagic model that will compare the ability of 3D TEE to identify changes in volume depletion and

repletion (EDV, ESV, EF) compared to the standard 2D TEE measurements of EDA, ESA and FAC. This study will also explore the utility of trans-mitral Doppler flow to examine what effect acute normovolemic hemodilution has on LV diastolic function. To date, there have been no studies investigating the quantification of 3D TEE LV volume with graded blood loss in the ANH human hemorrhagic model. Likewise, no data have been generated on the effects of ANH on diastolic function measured with trans-mitral Doppler flow.

Author Journal/Year	Model/ N	Measurements Used	Study Aim	Findings	Limitations/ Important Points
Urbanowicz JH et al, Anesthesiology, 1990	Human N=10	TEE: EDA, ESA, EFA; PAC: CO by thermodilution; Scintigraphy	Ability of TEE to estimate LV volume and ejection immediately after CABG surgery	Good correlation between EFA and scintigraphy ($r=0.82$)	1. Generalized only to CABG patients; 2. Early establishment of TEE's use in ICU; 3. Early comparative/validation study of TEE, PAC, scintigraphy
Clements FM, et al, BJA, 1990	Human N=26	TEE: EDA, ESA, EFA; Radionuclide angiography (RNA)	To correlate TEE to radionuclide angio. in estimating LV size and function	Good correlation found between EDV ($r=0.86$), ESV ($r=0.92$), and AEF ($r=0.96$) and RNA	Study established good correlation between TEE and RNA for assessing LV preload and function
Reich DL, Anesthesiology, 1993	Human (Pediatric) N=11 (3-15 Kg)	TEE: EDA SBP CVP	Ability of TEE to detect changes in cardiac filling during intraoperative manipulation of blood volume in pediatric cardiac surgical patients	CVP changes that are small (e.g.: 10mmHg to 9mmHg) may detect a significant change in BV that could go unnoticed	1. Can only be generalized to pediatric cardiac surgical patients; 2. Established TEE as a method for estimation of LV volume
Cahalan MK, et al, Anesthesiology, 1993	Human N=25	TEE by ABD of EDA, ESA, and FAC	Investigate whether ABD accurately estimates LV FAC, EDA, and ESA compared to off-line	1. ABD slightly underestimates EDA and slightly overestimates ESA and FAC 2. Requires quality images/user dependent	1. ABD may slightly underestimate preload; 2. ABD is dependent upon quality images throughout cardiac cycle for valid estim. of LV function

Author Journal/Year	Model/ N	Measurements Used	Study Aim	Findings	Limitations/ Important Points
Hwang JJ et al, Chest, 1993	Human N=80	TEE TTE	To evaluate TEE to TTE for the evaluation cardiac function in critically ill patients in ICU and ED	1. TEE safely provided critical information not able to be obtained by TTE; 2. TEE was valuable in assessing cardiac function and structural pathology	1. Provided safety and tolerability of TEE; 2. Early use of TEE in the ED; 3. Documented TEE efficacy when TTE unable to acquire images
Cheung AT et al, Anesthesiology, 1994	Human N=35	TEE: FAC PAC: PAOP CVP	Determine effects of acute graded hypovolemia on TEE and conventional hemodynamic determinants of LV preload in anesthetized patients with normal and abnormal LV function	LVEDA decreased linearly ($0.3\text{cm}^2/1\%$ EBV deficit) TEE and PAC indexes of preload had a threshold for detecting EBV of 2.5% (1.75ml/Kg)	1. Can only be generalized to cardiac patients. 2. Identifies TEE capable of monitoring blood loss.
Khoury AF et al, American Heart Journal, 1994	Human N=77	TEE, TTE	Review indications, feasibility, clinical impact of TEE compared to TTE in ICU patients	1. TEE able to acquire images when TTE is unable 2. TEE provides safe diagnostic tool	Established TEE as effective tool for its use in ICU
Morrissey RL et al, J American Society of Echocardiography, 1994	Animal (Dog) N=4	Open-chest: all chamber cannulated; TEE: ABD and off-line estim.	To determine the utility of ABD compared to off-line measurements of ESA, EDA, and FAC	Both ABD and off-line estimations correlated well with true volumes calculated by the open-chest model ($r=0.94$, $R=0.96$,	Provided early data re: correlation of ABD to off-line measurements compared to unique volume controlled model and early validity to ABD

				respectively)	
Author Journal/Year	Model/ N	Measurements Used	Study Aim	Findings	Limitations/ Important Points
Leung JM et al, Anesthesiology, 1994	Human N=139	TEE: EDA, ESA, FAC; HR, SBP, CVP, PAP	Investigate whether LV cavity obliteration during systole is indicative of hypovolemia in CABG patients	1. LV cavity obliteration is rarely preceded by changes in hemodynamic parameters 2. LV cavity oblit. is not frequently associated with ↓EDA	1. Describes qualitative evaluation of LV function often used intraoperatively 2. Not every instance of LV oblit. indicates ↓ LV filling 3. Sensitivity is 100%, however specificity is low due to high incidents of false- positive results 4. Practitioner must be aware of other reasons for ↓ in LV EDA (changes in contractility or afterload)

Heidenreich PA et al, J American College of Cardiology, 1995	Human N=61	TEE TTE	1. Study of ICU patients with unexplained hypotension >60 minutes with both TEE and TTE 2. Establish TEE as a predictor of mortality in those with patients with non-ventricular cardiac limitations	TEE diagnoses of non-vent. limitation of CO was associated with improved survival (81%) compared to diag. of vent. disease (41%); those with hypovolemia/↓ SVR was 44% improved survival 2. TEE outperformed TTE in image acquis.	1. Early determination of TEE's ability to diagnose LV etiology of hypotension in ICU 2. Predictive model 3. Establishes TEE as a valid method for guiding decision-making in the ICU
Author Journal/Year	Model/ N	Measurements Used	Study Aim	Findings	Limitations/ Important Points
Perrino AC et al, Anesthesiology, 1995	Human N=16	TEE by ABD estimates of ESA, EDA, FAC; TEE off-line of ESA, EDA, FAC	Comparison of ABD of LV function to off-line TEE measurements in non-cardiac surgical patients	1.High correlation between ABD and off-line measurements of ESA (r=0.93), EDA (r=0.89) and FAC (r=0.90) 2. High accuracy of 96% in tracking serial LV changes	1. Small systematic underestimation of FAC by ABD 2. Accuracy of ABD reported 3. Helps to define ABD as accurate estimate of LV preload 4. Highly dependent on quality images and experience of user

Swenson JD, Anesthesiology, 1996	Animal (dog) N=5	TEE: ABD; PAC: PAOP, CO, LVSW; CVP	TEE using ABD to detect if EDA can identify an appropriate end-point for IV fluid administration	TEE was used to assess resuscitation and not used to grade exsanguinations. LVSW (grams-meters) = SV (MAP-PCWP) x 0.0136	1. Animal model with only 5 dogs 2. Used TEE to guide fluid replacement not removal 3. Only study to use ABD
Author Journal/Year	Model/ N	Measurements Used	Study Aim	Findings	Limitations/ Important Points
Liu N et al, Anesthesiology, 1996	Human N=10	TEE: ABD Radionuclide angiography (RNA) of LV	Compare ABD with simultaneous RNA in critically ill ICU patients to obtain a quantifiable method of LV function	1. Good correlation between simultaneous estimations of LV EF by RNA (55%) and FAC by ABD (46%, r=0.85) 2. FAC by ABD may be used at the bedside for evaluating LV function	1. FAC by ABD continues to be validated by this study 2. ABD is dependent on proper lateral gain settings to ensure high image quality 3. ABD is able to give a real-time evaluation of LV function

Grandi AM et al, Cardiology, 1997	Human N=20	TEE: ABD	To test the clinical feasibility of TEE using ABD to detect small changes in preload with position changes and tourniquets on all four extremities using healthy male volunteers	Small changes in blood return to the heart with position change (elevated legs) or tourniquet use caused changes in EDA and ESA	<ol style="list-style-type: none"> 1. Provides data on healthy volunteers as compared to most studies that use cardiac patients 2. Identifies TEE (ABD) as a sensitive indicator of LV volume
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Author Journal/Year	Model/ N	Measurements Used	Study Aim	Findings	Limitations/ Important Points
Suriani RJ et al, J Cardiothoracic and Vascular Anesthesia, 1998	Human N=68	TEE: qualitative and off-line; PAC; CVP	Study the impact of TEE in non-cardiac surgery both in a consultative and non-consultative cases	<ol style="list-style-type: none"> 1. TEE identified intraoperative pathology and reasons for LV dysfunction 2. Majority of use was for LV dysfunction 3. General surgical service requested most TEE in major abdominal cases 4. Higher ASA physical acuities (III and IV) used TEE more often 5. Patients older than 66 years required more TEE consultations than younger patients 	<ol style="list-style-type: none"> 1. TEE is called on for intraoperative consult. and evaluation of LV function by non-TEE trained anesthiol. 2. Provides surgical services and types of cases that TEE may be used for consults 3. Higher ASA classes are more likely to need TEE consultation 4. Older patients are at higher risk of needing TEE evaluation of LV function 5. Provides the first study of a need for TEE by type of surgical service, a particular type of surgical cases, ASA classification and age
Kolev N et al, Anaesthesia, 1998	Human N=224	TEE; qualitative and off-line; HR, ECG, ABP, PAC	<ol style="list-style-type: none"> 1. Role of TEE in intraoperative decision-making compared with other measures of hemodynamics 2. Types of cases TEE used based on ASE 	<ol style="list-style-type: none"> 1. Fluid evaluation and bolusing most reason for TEE 2. TEE influential in guiding decision-making in category II criteria of indications 	<ol style="list-style-type: none"> 1. European multicenter study 2. Provided insight into reasons for TEE intraoperatively 3. Describes which category criteria for

Author Journal/Year	Model/ N	Measurements Used	Study Aim	Findings	Limitations/ Important Points
Dalibon N, British Journal of Anaesthesia, 1999	Animal (pig) N=18	MAP PCWP Systolic Arterial Pressure (SAP): Δ Down TTE: LVEDA	Compare frequently used measures of blood volume assessment during progressive hemorrhage and resuscitation	3. More frequent management changes in category I criteria Blood removed in 7 steps (total 35ml/Kg) at 5ml/Kg per step. Suggests that no single variable is sufficient for precise assessment of BV loss.	TEE use are used 1. Used TTE, not TEE. 2. Animal model
Tousignant CP et al, Anesthesia and Analgesia, 2000	Human N=41	TEE off-line; PAC: PCWP	Investigate relationship between SV and EDA in response to a fluid challenge of 500ml pentastarch in critically ill ICU patients; responders increased their SV by 20%	1. Responder to fluid had lower EDA and PCWP than the non-responders 2. Only responder EDA increased with fluid administration 3. No optimum EDA was identified 4. Moderate correlation between SV and EDA ($r=0.60$)	1. Provides a relation between those with low EDA to increase their preload and SV by 20% 2. Those patients with LV dysfunction reported larger EDA and elevated PCWP 3. Illustrates lack of correlation between EDA and PCWP
Colreavy FB et al, Critical Care Medicine, 2002	Human N=255	TEE: off-line after qualitative evaluation	To evaluate the safety and utility of TEE performed on critically ill patients in the ICU	1. Hypotension: most common reason 2. In 67% of the hypotensive patients, TEE revealed etiology 31% of the time 3. TEE findings led to significant	1. Provides continual review of TEE as a method for rapid evaluation of hypotensive patients 2. Hemodynamically unstable patients can be evaluated and a

				management changes in 32% of the patients	significant number managed with TEE
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Table 2.3. Chronological listing of literature regarding use of transesophageal echocardiography in left ventricular assessment of function and volume determination.

Methods

Study Design Overview

This prospective, non-randomized experimental study enrolled patients scheduled for elective open radical prostatectomy or anterior/posterior spinal fusion, which included routine acute normovolemic hemodilution (ANH) as a controlled human hemorrhagic model. The purpose of this study was to determine if selected measurement methods obtained by transesophageal echocardiography (TEE) were reliable for detecting changes in left ventricular volume and function associated with blood loss and replacement.

Hypotheses

Hypothesis 1: there will be no statistically significant differences among the mean values of LVEDA, LVESA, and FAC measurements by two-dimensional TEE across the seven conditions of graded blood removal and replacement with Hextend®.

Hypothesis 2: there will be no statistically significant differences among the mean values of LVEDV, LVESV, and EF measurements by three-dimensional TEE across the seven conditions of graded blood removal and replacement with Hextend®.

Hypothesis 3: there will be no statistically significant differences among mean values between two-dimensional LVEDA, LVESA, and FAC and three-dimensional measurements of LVEDV, LVESV, and EF across the seven conditions of graded blood removal and replacement with Hextend®.

Hypothesis 4: there will be no significant correlations found between the two-dimensional measurements of LVEDA, LVESA, and FAC and three-dimensional

measurements of LVEDV, LVESV, and EF at each of the seven conditions of graded blood removal and replacement with Hextend®.

Hypothesis 5: there will be no statistically significant differences in TEE mean values of E and A wave morphology acquired by trans-mitral Doppler flow measurements across the seven conditions of graded blood removal and replacement with Hextend®.

Subjects and Setting

Following institutional human subjects research committee approval from both the University of California San Francisco and University of California Davis, written, informed consent was obtained by the researcher from each of the patients scheduled for elective open radical prostatectomy or anterior/posterior spinal fusion at the University of California Davis Medical Center (UCDMC) where ANH is a routine part of the perioperative strategy to minimize the need for heterologous blood transfusion. The staff surgeons in urology and orthopedic spine at UCDMC provided the patient population. Patients who met the inclusion criteria of the UCDMC ANH protocol (Appendix 4) were given information regarding the study at their preoperative surgery clinic visit by the researcher, and informed consent was obtained at that time. Participants were given the researcher's pager number if any further information was needed prior to the surgery. The researcher met each patient in the preoperative area the day of surgery to discuss any questions regarding the study.

Inclusion criteria comprised the following: all patients who were scheduled for elective open radical prostatectomy or anterior/posterior spinal fusion where ANH was part of the perioperative plan and met the selection standards for ANH. Exclusion criteria

included the following: (1) patients where ANH is contraindicated (advanced age >70 years, hematocrit <30 gm/dl) or esophageal pathology (diverticulae, hiatal hernia, esophageal cancer, esophageal surgery) that could introduce risks associated with the placement of the ultrasound transducer; (2) patients with severe or symptomatic COPD, emphysema, renal, hepatic or coronary artery disease as defined by the American College of Cardiology (Cannon et al., 2001)

The sample power for this study was set at 0.80 with a two-tailed alpha of 0.05. An effect size of 0.5 of the standard deviation was based on previously established data measurements of EDA and ESA previously described by Cheung (Cheung, et al, 1994). A value of $p < 0.05$ was considered statistically significant to detect a difference in means across the four conditions of the repeated measures for blood removal and three conditions of colloid replacement. Calculations for the number of patients needed in this study ($n = 33$) were achieved using nQuery® in a one-way analysis of variance (ANOVA) for repeated measures. However, 40 patients were planned to be enrolled in order to ensure that complete data from the required number of patients was obtained and appropriate statistical power achieved.

Measurements

Two-dimensional TEE images were obtained using the Siemens Sequoia Cardiovascular System Model #C512 with the V5M transesophageal probe (Siemens Medical Solutions, Malvern, PA). The long axis view of the left ventricle was obtained with the TEE probe positioned in the mid-esophageal two-chamber view (ME 2CH). Care was taken to optimize LV chamber size and avoid foreshortening. The probe was then rotated to position the left atria and ventricle in the center of the imaging plane.

Three-dimensional software was then used to acquire 180° of 2D images of the heart at 5° intervals (total of 26 images). These images were then stored for off-line 3D reconstruction and assessment of EDV, ESV, and EF using proprietary software, Research Arena™ (TomTec Imaging Systems, Unterschleissheim, Germany).

With the TEE probe in the same ME 2CH view, LV diastolic function was assessed using pulsed wave Doppler echocardiography of the mitral flow velocities. Color flow Doppler imaging was used prior to trans-mitral flow measurements to detect any unsuspected mitral valvular disease. For consistency, the pulsed wave trans-mitral Doppler flow velocity measurements were obtained with the cursor placed at the tip of the mitral valve leaflets, which is consistent with institutional practice and described by others (Lattik et al., 2002). After the trans-mitral Doppler flow image was optimized, a still image store was obtained for off-line characterization of the flow patterns. The comprehensive evaluation of LV function included E-wave amplitude, A-wave amplitude, and E/A wave ratio and additional measurements of E-deceleration time, A-deceleration time, and time-velocity integral (TVI) for both waves. The TEE probe was then advanced into the stomach and ante-flexed to acquire the trans-gastric short axis view (TG SAX) of the left ventricle. For consistency, the images were acquired at the level of the papillary muscles and a 3 second video clip was stored. Measurements of EDA, ESA, and FAC were calculated manually off-line. Fractional shortening (FS), manually acquired from the TG SAX view, was derived from measurements between the anterior and inferior endocardial boarder of the left ventricular chamber internal diameter in diastole (LVIDD) and systole (LVIDS).

At the conclusion of each study, all TEE measurements were transferred from the internal hard drive of the Siemens Sequoia machine to a magnetic optical cassette for storage and off-line assessment by the researcher. Standard continuous perioperative monitoring included non-invasive blood pressure, mean arterial pressure, heart rate, ECG (leads II and V₅), pulse oxymetry, temperature, and end-tidal CO₂. Arterial pressure cardiac output was monitored with the Vigileo and *FloTrac* Sensor (Edwards Lifesciences LLC, Irvine, CA). A study design overview is provided in Table 1.

Procedures

Prior to the start of the study, all pertinent demographic and preoperative medical data including allergies, current medications, and preoperative medical conditions were documented on the patient data flow sheet developed by the researcher. To limit potential confounders associated with the use of different anesthesia providers and anesthetic techniques, four anesthesia providers (two anesthesiologists and two nurse anesthetists) who were familiar with the study design but were not co-investigators were assigned the responsibility of perioperative anesthetic management of the patient. This ensured that two of the four (one anesthesiologist and one nurse anesthetist) would be available on the day of the study. The protocol standardized the anesthetic medication administered and was calculated based on patient's weight. Midazolam (0.01-0.02 mg/kg) was given as a routine preoperative sedative. The patient was brought to the OR and the standard monitors applied. Intrathecal morphine (0.25 mg-0.40 mg) was administered with the patient in the sitting position. After the completion of the intrathecal morphine, the patient was placed in the supine position and pre-oxygenation begun. Fentanyl (1-3 mcg/kg) was administered prior to induction of general anesthesia. Induction of general

anesthesia was achieved with Propofol (1-2.5 mg/kg). Neuromuscular blockade was established with Rocuronium (1.0 mg/kg) to facilitate endotracheal intubation and provide muscle relaxation during the surgery. General anesthesia was maintained with the volatile agent Sevoflurane in an air/oxygen mixture to achieve a fractional inspired oxygen concentration (FiO_2) of 0.6.

After general anesthesia was induced and the airway secured with an endotracheal tube, a large-bore intravenous catheter was placed in the basilic or external jugular vein as per the institutional standardized ANH procedure (Appendix 4). A radial arterial catheter was then placed to provide continuous blood pressure measurements. In addition the arterial catheter allowed for blood gas and hematocrit analysis at baseline, after 15% removal of blood, and after re-infusion of the 15% blood loss with Hextend[®]. A #18 Fr. orogastric tube was inserted in to the esophagus prior to the TEE probe to remove any air or gastric contents and enhance TEE image acquisition. The TEE probe was then placed into the esophagus following the established standard technique (Thys, 1996). Estimated blood volume was calculated using the standard formula of 70ml/kg for males and 65ml/kg for females as used in previously similar work (Cheung, 1994). During this time, the surgical team positioned the patient for their respective procedure (supine for prostatectomy and right lateral decubitus for anterior/posterior spine). After positioning, the patient was prepped and draped for their procedure. Surgical incision was consistently made during the blood removal phase and the completion of the study was generally one hour after induction of anesthesia and line placement. The surgical times were consistent, depending on the procedure with prostatectomy times of 3 hours and the anterior portion

of the anterior/posterior procedures of 4 hours. Total surgical time for the anterior/posterior procedure was generally 10 hours.

After the initial baseline measurements were obtained, 15% of the patient's calculated total blood volume was removed via the large-bore intravenous catheter. The blood was removed in 5.0% aliquots until a total of 15% was obtained. Removed blood was stored in reservoir blood bags containing the anticoagulant citrate-phosphate-dextrose (CPD) solution (Baxter Healthcare Corp., Deerfield, IL) to prevent clotting, marked with the patient's information, and kept in the OR at room temperature until re-infused. The time for each aliquot of blood to be removed was approximately 10 minutes. TEE measurements were repeated following each 5.0% aliquot removal while continuous ECG, arterial blood pressure, heart rate, pulse oxymetry, end-tidal carbon dioxide, and temperature were monitored to assess the patient's response to the blood removal. Re-establishment of the intravascular volume was then begun and accomplished with an equivalent amount of the colloid Hextend[®]. TEE measurements were repeated during the volume replacement phase, again in three 5.0% increments, until the intravascular volume was returned to the pre-ANH baseline measurements (A1-A3, Table 3.1). If the patient became hemodynamically unstable any time during the blood removal or replacement as evidenced by ischemic changes on the ECG, segmental wall motion abnormality on TG SAX TEE, increased heart rate (greater than 10 beats per minute), or hypotension (greater than 15% drop in blood pressure), appropriate management was immediately initiated with a phenylephrine infusion initially set at 0.1 mcg/Kg/min. Adjustments made to the infusion were made by the primary anesthesia team caring for

the patient to maintain a MAP >50mmHg. Infusions were tapered and stopped when the MAP was >60mmHg.

To examine both the stability of the TEE measurements and the effects of general anesthesia over time, 5 patients undergoing prostatectomy served as controls. During the hemodynamically stable period that occurs after the induction of general anesthesia, TEE images were obtained and recorded for 40 minutes. TEE measurements for the control patients were examined at baseline and at two twenty-minute intervals. After the data collection was completed, these patients underwent ANH.

Approximately 10 minutes after the induction of general anesthesia, baseline echocardiographic data collection occurred. Data from each of the measurement times took approximately 7-10 minutes each to obtain. Therefore, the total time to acquire the hemodilution data (R0-R3, Table 3.1) was approximately 30 minutes. Data from the re-establishment of intravascular volume (A1-A3, Table 3.1) required approximately 15 minutes to acquire. Re-infusion with Hextend[®] was facilitated with the Belmont rapid infusion device (Belmont Instrument Corporation, Billerica, MA). The total time to complete the study was approximately one hour. At each data collection point (R0 through A3) hemodynamic recordings were documented on a data flow sheet. A copy of the anesthesia record, arterial blood gas and electrolyte results were placed in the patient data file, which provided intraoperative documentation of all anesthetic agents, medications, intravenous fluids given, blood loss, urine output, and any other interventions given to the patient during the study period.

Preliminary analyses of the data collected from the first 20 patients were analyzed to identify any trends or untoward effects to the patients.

Off-line TEE Measurements

Two-dimensional data previously stored on magnetic optical discs were analyzed using the Siemens Sequoia Cardiovascular System Model #C512 (Siemens Medical Solutions, Malvern, PA). Fractional shortening (FS) was acquired by measuring the LVIDD and LVIDS of the anterior and inferior epicardial borders with the TEE probe in the TG SAX position. Three independent measurements were taken for each three-second video loop across all seven conditions. The average of the three measurements for each condition was used for the statistical analysis. Likewise, the average FAC was obtained by measuring the EDA and ESA in the TG SAX view at the level of the papillary muscles with three repeated measures across the same three-second video loop.

Three-dimensional data previously stored on a magnetic optical disc were analyzed with the proprietary software *fourSight*[™] (Research Arena[™], TomTec Imaging Systems, Unterschleissheim, Germany). Images were transferred from the magnetic optical disc to a computer in the Department of Cardiology where the proprietary software was available. The EF was obtained by a series of steps beginning with the centering of the LV chamber in orthogonal alignment for maximal visualization. Volumetric assessment of the LV EDV, ESV was acquired by drawing the epicardial border in each phase of relaxation and contraction. To optimize the calculated volume, three orthogonal positions were obtained with each measurement taken at forty-five degrees from the previous measurement. The estimation of EDV, ESV, and EF were repeated across the seven conditions for each subject.

Trans-mitral Doppler flow data, also stored on magnetic optical disc, were assessed with the Siemens Sequoia Cardiovascular System Model #C512 (Siemens

Medical Solutions, Malvern, PA). Measurements of E-wave, A-wave, and E/A wave ratio in addition to E and A-wave acceleration, deceleration, volume-time integer, and slope were obtained on three separate E and A waves on each stored clip file across all seven conditions. The average of three measurements for each Doppler flow image was used in the statistical analysis.

Data Analysis

Data management and statistical analysis was achieved with SPSS[®] 14 software (SPSS, Inc., Chicago, IL). The results of the data obtained across the seven conditions measured are reported with their means, \pm SD, or \pm SEM where appropriate. For the evaluation of changes over time, the classic repeated measures analysis of variance (RM-ANOVA) was replaced with the mixed models repeated measures ANOVA. This newer technique allows subjects with missing data points to contribute their available data to the analysis. In the classic ANOVA, those patients with missing data would have been eliminated from the analysis.

Hypothesis 1: Mixed models for repeated measures of analysis of variance (MM RM-ANOVA) was used to determine if statistically significant differences were present among the mean values of LVEDA, LVESA, and FAC measurements by two-dimensional TEE across the seven conditions of graded blood removal and replacement with Hextend[®].

Hypothesis 2: Mixed models for RM-ANOVA was used to determine if statistically significant differences were present among the mean values of LVEDV, LVESV, and EF measurements by three-dimensional TEE across the seven conditions of graded blood removal and replacement with Hextend[®].

Hypothesis 3: A two-way MM RM-ANOVA was used to determine if statistically significant differences were present among mean values between two-dimensional LVEDA, LVESA, and FAC and three-dimensional measurements of LVEDV, LVESV, and EF across the seven conditions of graded blood removal and replacement with Hextend[®].

Hypothesis 4: Pearson's Product, Moment Correlation was used to determine the relationship between the two-dimensional measurements of LVEDA, LVESA, and FAC and three-dimensional measurements of LVEDV, LVESV, and EF at each of the seven conditions of graded blood removal and replacement with Hextend[®].

Hypothesis 5: Mixed models RM-ANOVA was used to determine if statistically significant differences were present in TEE mean waves of E-wave, A-wave, and E/A wave ratios acquired by trans-mitral Doppler flow velocity measurements across the seven conditions of graded blood removal and replacement with Hextend[®].

STUDY DESIGN OVERVIEW

DEMOGRAPHICS	DATA COLLECTED
Age	Preoperatively
Gender	Preoperatively
Height	Preoperatively
Weight	Preoperatively
Body Mass Index	Preoperatively
Current Medications	Preoperatively
Co-existing Diseases	Preoperatively
Allergies	Preoperatively
Smoking History	Preoperatively
Alcohol Use	Preoperatively
Illicit Drug Use	Preoperatively

DEPENDENT VARIABLES	TIME OF DATA COLLECTION	CONDITIONS						
		<i>Baseline</i>	<i>R-5%</i>	<i>R-10%</i>	R15%	A-10%	A-5%	Final
2-D LVEDA	At measurement	✓	✓	✓	✓	✓	✓	✓
2-D LVESA	At measurement	✓	✓	✓	✓	✓	✓	✓
2-D FAC	At measurement	✓	✓	✓	✓	✓	✓	✓
3-D LVEDV	At measurement	✓	✓	✓	✓	✓	✓	✓
3-D LVESV	At measurement	✓	✓	✓	✓	✓	✓	✓
3-D LVEF	At measurement	✓	✓	✓	✓	✓	✓	✓
Trans-Mitral Flow	At measurement	✓	✓	✓	✓	✓	✓	✓
ADDITIONAL DATA COLLECTED								
Systolic Blood Pressure	Continuous	✓	✓	✓	✓	✓	✓	✓
Diastolic Blood Pressure	Continuous	✓	✓	✓	✓	✓	✓	✓
Mean Arterial Blood Pressure	Continuous	✓	✓	✓	✓	✓	✓	✓
ECG/Heart Rate/O ₂ Sat.	Continuous	✓	✓	✓	✓	✓	✓	✓

Table 3.1. Study Design Overview

LVEDA: Left ventricular end diastolic area

LVESA: Left ventricular end systolic area

FAC: Fractional Area Change

LVEF: Left ventricular ejection fraction

R: Removal of blood in 5% aliquots

A: Addition of Hextend® for re-establishment of blood volume in 5% aliquots

✓ : Identifies measures to be documented with each 5% aliquot of blood removed and replacement with Hextend®

Results

Patient Study Population Overview

Forty-seven patients were recruited and invited to participate in this study. Two patients refused to participate at the time of their recruitment at the Department of Urology Surgery Clinic. In addition, one patient from the anterior-posterior spine patient group had his procedure changed to a posterior fusion only on the day of his surgery making him ineligible to participate. One patient from the prostatectomy group was unable to be studied the day of his surgical procedure due to an inability to obtain the specific TEE machine needed for the study from the Department of Cardiology. Of the forty-three patients studied, five served as a control group to characterize anesthetic related changes in hemodynamic and left ventricular function over time. Thirty-eight patients served as the study population. Of those 38 patients, five patient data sets were lost to the final analysis for a variety of reasons. The surgical procedures of two prostatectomy patients early in the study were done with robotic assistance making their TEE images difficult to acquire (study patients #1 and #2). This was due to the fact that patients undergoing robotic assisted prostatectomy are positioned in steep Trendelenberg. This position made it difficult to position the TEE probe within the esophagus to obtain cardiac images, especially in the trans-gastric short axis view. Another two patients were eliminated from the study because of logistical issues with the TEE machine on loan from the Department of Cardiology (study patients # 13 and #27) and one patient was removed from statistical analysis due to the extravasation of an unknown quantity of Hextend[®] from the intravenous catheter into the interstitial tissue (study patient #28). After the

losses to the analysis described above, 33 patient data sets were evaluated. Demographic information for both the study and control groups is listed in Table 4.1 and no statistically significant differences were noted between groups.

Demographic	Prostatectomy Group Mean (SD)	Anterior/Posterior Spine Group Mean (SD)	Total Study Group Mean (SD)	Control Group Mean (SD)
N	27	6	33	5
Age	59.37(4.69)	50.17(9.0)	57.70 (6.612)	59 (6.8)
Height (cm)	176.18(7.75)	164.50(7.56)	174.06 (8.870)	179.60 (6.189)
Weight (kg)	88.70(14.13)	75.17(7.81)	86.24 (14.136)	92.2 (29.423)
BMI	28.55(4.87)	27.83(3.97)	28.42 (4.671)	28.40 (9.343)

Table 4.1. Mean and standard deviation of the demographic data for study and control groups

Review of Data Analysis

As previously described, the sample power for this study was set at 0.80 with a two-tailed alpha of 0.05. An effect size of 0.5 of the standard deviation was based on previously published work by Cheung and colleagues on the measurements of EDA, ESA, and FAC in cardiac surgical patients during graded blood removal (Cheung et al., 1994). Statistical significance was set at $p < 0.05$ to detect a difference in mean scores across four conditions of the repeated measures for blood removal and three conditions of volume replacement with the colloid, Hextend[®]. Calculations for the number of patients needed to attain statistical significance were achieved with nQuery[®]. SPSS[®] version 14 (Chicago, IL) was used for statistical analysis of the data. A newer technique for the analysis of variance was utilized for the data analysis. Mixed models repeated measures analysis of variance (RM-ANOVA) was used because unlike the standard RM-ANOVA that eliminates a subject from the analysis if there are missing data, mixed models RM-ANOVA allows each subject in the study to contribute their data for analysis. Three patients (Patients #6, #8, #11) had one missing data point in the 2D data sets, and two

patients (Patients #7, #38) had one missing data point in the trans-mitral data sets. In the 3D data sets, however, missing data points were more frequent resulting in 29 of the 33 patients contributing data for analysis. The 3D data of four patients (Patients #15, #30, #35, #36) were completely eliminated from the mixed models analysis because their 3D reconstruction images were unable to be analyzed for various reasons that will be discussed in the following chapter. Of the 29 patients that were analyzed with mixed models RM-ANOVA, missing data points were spread across the seven conditions measured: Baseline = 3 (Patients #3, #5, #7), R-5% = 4 (Patients #5, #6, #19, #21), R-10% = 2 (Patients #12, #19), R-15% = 4 (Patients #9, #17, #19, #37), A-10% = 2 (Patients #7, #17), A-5% = 2 (Patients #7, #10), and Final = 2 (Patients #5, #8).

One-Dimensional TEE Results

Although one-dimensional left ventricular chamber analysis was not included in the hypotheses, their data are reported here for a more complete characterization of graded hypovolemia and volume replacement among the various methods of LV chamber measurement. As previously reported by Cheung and colleagues in their work on hemodilution in cardiac surgical patients, all measurements of left ventricular dimensions detect similar changes in chamber size (Cheung et al., 1994).

The data from 33 patients were analyzed for changes in the one-dimensional measurements of left ventricular end-diastolic diameter (EDD), end-systolic diameter (ESD), and fractional shortening (FS). Statistically significant changes from baseline were detected in EDD ($p < .001$) and ESD ($p < .001$) measurements across the six conditions of three aliquots of 5% graded hemodilution and three aliquots of 5% volume

replacement with Hextend[®]. There were no statistically significant changes in FS during graded blood removal and replacement (Table 4.2).

Source	Significance (p)	F	N
EDD	< .0001	18.814	33
ESD	< .0001	6.775	33
FS	.371	1.125	33

Table 4.2. Tests of fixed effects reported on EDD, ESD, and FS. Significance at $p < .05$.

End-diastolic diameter mean values with their corresponding standard error and confidence intervals are reported in Table 4.3. From a mean baseline measurement of 4.3 ± 0.11 cm, decreases in EDD were noted throughout the blood removal phase to 3.7 ± 0.12 cm at R-15%. Increases in EDD were observed during re-infusion. Mean EDD diameter at A-10% was 4.0 ± 0.11 cm and increased to the baseline EDD value at A-5% of 4.3 ± 0.10 cm increasing to a final mean value of 4.4 ± 0.09 cm.

Condition	Mean (cm)	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	4.3	.11	4.2	4.6
R-5%	4.1	.12	3.9	4.4
R-10%	4.0	.12	3.8	4.3
R-15%	3.7	.12	3.5	4.0
A-10%	4.0	.11	3.8	4.3
A-5%	4.3	.10	4.2	4.6
Final	4.4	.09	4.3	4.6

Table 4.3. Mean values, standard error, and 95% confidence intervals for EDD.

Using Mixed Models ANOVA, statistically significant changes were identified among the mean values of EDD ($p < .0001$). Post Hoc analysis using Bonferroni pairwise comparisons was performed for the dependent variable, EDD, to determine where in the 6 conditions a statistically significant difference among mean values occurred when compared to the baseline measurement (Table 4.4).

Condition	Condition	Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
					(cm)	(cm)
R-5%	Baseline	-.27(*)	.088	.026	-.52	-.02
R-10%	Baseline	-.39(*)	.082	< .0001	-.62	-.15
R-15%	Baseline	-.61(*)	.083	< .0001	-.85	-.38
A-10%	Baseline	-.32	.125	.091	-.67	.03
A-5%	Baseline	-.01	.120	1.000	-.35	.34
Final	Baseline	.07	.091	1.000	-.18	.33

Table 4.4. Bonferroni Post Hoc pairwise comparisons shown for EDD. Based on estimated marginal means. R: removal of blood during ANH, A: addition of colloid during re-infusion of Hextend®

* The mean difference is significant at the .05 level.

Statistically significant differences were observed in the EDD of the left ventricle during the removal of blood in 5% aliquots for the initial phase of acute normovolemic hemodilution (ANH). The mean difference between baseline and R-5% was $-0.27 \pm 0.088\text{cm}$ ($p = .026$). This statistically significant difference continued throughout the blood removal phase with values of $-0.39 \pm 0.082\text{cm}$ ($p < .0001$) and $-0.61 \pm 0.083\text{cm}$ ($p = .0001$) between R-10% and R-15%, respectively. During the second phase of ANH, EDD was returned to near baseline measurements by A-5% and no statistically significant changes in the mean dimensions were measured throughout the re-establishment of intravascular volume with Hextend® between baseline and A-10% ($-0.32 \pm 0.125\text{cm}$, $p = .091$), baseline and A-5% ($-0.01 \pm 0.120\text{cm}$, $p = 1.000$), and baseline and final ($0.07 \pm 0.091\text{cm}$, $p = 1.000$).

Like EDD, ESD was demonstrated to have a statistically significant difference ($p < .0001$) in mean systolic diameter during removal and replacement with colloid (Table 4.2). The ESD mean values, standard error and 95% confidence intervals across the 7 measured conditions are provided in Table 4.5. From the baseline mean value of $2.5 \pm 0.12\text{cm}$, a decrease in mean ESD dimension was observed during blood removal at each

5% aliquot to an EDD of $2.1 \pm 0.09\text{cm}$ at R-15%. Increases in ESD measurements were noted during re-infusion at each 5% increase in volume. A smaller change in ESD was noted between mean values of $2.1 \pm 0.12\text{cm}$ at A-10% and the final measurement of $2.4 \pm 0.10\text{cm}$ when compared to the difference in the mean values of $2.1 \pm 0.12\text{cm}$ at A-10% and $2.3 \pm 0.10\text{cm}$ at A-5%.

Condition	Mean (cm)	Std. Error (cm)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	2.5	.12	2.3	2.6
R-5%	2.3	.13	2.1	2.6
R-10%	2.3	.12	2.0	2.5
R-15%	2.1	.09	1.9	2.3
A-10%	2.1	.12	1.9	2.4
A-5%	2.3	.10	2.1	2.5
Final	2.4	.10	2.2	2.6

Table 4.5. Mean values, standard error, and 95% confidence intervals for ESD.

Mixed Models ANOVA demonstrated a statistically significant difference in mean values for ESD ($p < .0001$). Post Hoc analysis with Bonferroni pairwise comparisons was also performed for the dependent variable, ESD, to determine where in the 6 conditions a statistically significant difference among mean values occurred when compared to the baseline measurement (Table 4.6).

Condition	Condition	Mean Difference (cm)	Std. Error (cm)	Sig. (p)	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
R-5%	Baseline	-.17	.091	.400	-.43	.09
R-10%	Baseline	-.25(*)	.085	.039	-.49	-.01
R-15%	Baseline	-.42(*)	.088	< .0001	-.66	-.17
A-10%	Baseline	-.36(*)	.126	.049	-.71	-.001
A-5%	Baseline	-.19	.104	.522	-.48	.11
Final	Baseline	-.11	.104	1.000	-.40	.18

Table 4.6. Bonferroni Post Hoc pairwise comparisons shown for ESD. Based on estimated marginal means. R: removal of blood during ANH, A: addition of colloid during re-infusion of Hextend®
* The mean difference is significant at the .05 level.

Statistically significant changes in mean difference were noted between baseline and R-10% ($-.25 \pm 0.085\text{cm}$, $p = .039$), baseline and R-15% ($-.42 \pm 0.088\text{cm}$, $p < .0001$), and baseline and A-10% ($-.36 \pm 0.126\text{cm}$, $p = .049$). Small differences in mean values between baseline and R-5% ($-.17 \pm 0.091\text{cm}$, $p = .400$), baseline and A-5% ($-.19 \pm 0.104\text{cm}$, $p = .522$), and baseline and final ($-.11 \pm 0.104\text{cm}$, $p = 1.000$) were not statistically significant.

Fractional shortening was examined for changes in mean values across the seven conditions of blood removal and replacement with Hextend[®] during ANH. Mean values, standard error and 95% confidence intervals across the 7 measured conditions for FS are represented in Table 4.7. Changes in the mean values of FS were noted to be minimal from baseline ($.437 \pm 0.017\text{cm}$) through the final measurement ($.466 \pm 0.019\text{cm}$). No statistical significance was noted among the mean values across the seven conditions of blood removal and replacement ($p < .371$).

Condition	Mean (cm)	Std. Error (cm)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	.44	.02	.40	.47
R-5%	.44	.02	.41	.48
R-10%	.44	.02	.40	.48
R-15%	.45	.02	.41	.48
A-10%	.48	.02	.43	.52
A-5%	.47	.02	.43	.51
Final	.47	.02	.43	.50

Table 4.7. Mean values, standard error, and 95% confidence intervals for FS.

Two-Dimensional TEE Results

Hypothesis 1 stated that there would be no statistically significant differences among the mean values of LVEDA, LVESA, and FAC measurements by two-dimensional TEE across the seven conditions of graded blood removal and replacement.

Data from 33 patients were analyzed for changes in left ventricular end-diastolic area (EDA) end-systolic area (ESA), and fractional area change (FAC). Two-dimensional TEE measurements of EDA and ESA demonstrated a statistically significant change from baseline during 5% graded hemodilution and volume replacement with Hextend® across the six conditions measured. However, there were no statistically significant changes in FAC during graded blood removal and replacement (Table 4.8).

Source	Significance (p)	F	N
EDA	< .0001	26.515	33
ESA	< .0001	6.426	33
FAC	.369	1.028	33

Table 4.8. Tests of fixed effects reported on EDA, ESA, and FAC. Significance at $p < .05$.

The EDA mean values, standard error and 95% confidence intervals across the 7 measured conditions are presented in Table 4.9. From the mean baseline measurement of $13.8 \pm 0.47\text{cm}^2$, changes in EDA were noted throughout blood removal down to $10.9 \pm 0.44\text{cm}^2$ (R-15%). During the re-infusion phase, mean EDA measurements detected a difference from baseline in LV area through A-5% ($13.8 \pm 0.51\text{cm}^2$). There were no differences in EDA measurements between A-5% and Final ($13.8 \pm 0.39\text{cm}^2$).

Condition	Mean (cm^2)	Std. Error (cm^2)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	13.8	.47	12.8	14.7
R-5%	12.4	.53	11.3	13.5
R-10%	11.9	.46	11.0	12.9
R-15%	10.9	.44	10.0	11.7
A-10%	12.4	.53	11.3	13.5
A-5%	13.8	.51	12.8	14.8
Final	13.8	.39	13.0	14.6

Table 4.9. Mean, standard error, and 95% confidence intervals for EDA.

Mixed Models ANOVA demonstrated statistically significant differences in mean EDA values ($p < .0001$). Post Hoc analysis using Bonferroni pairwise comparisons was

performed for the dependent variable, EDA, to determine where in the 6 conditions a statistically significant differences among mean scores occurred when compared to the baseline measurement (Table 4.10).

Condition	Condition	Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
					(cm ²)	(cm ²)
R-5%	Baseline	-1.4(*)	.37	.005	-2.5	-.351
R-10%	Baseline	-1.8(*)	.37	<.0001	-2.9	-.791
R-15%	Baseline	-2.9(*)	.35	<.0001	-3.9	-1.927
A-10%	Baseline	-1.4	.59	.154	-3.1	.28
A-5%	Baseline	.03	.508	1.000	-1.4	1.5
Final	Baseline	.03	.447	1.000	-1.2	1.3

Table 4.10. Bonferroni Post Hoc pairwise comparisons shown for EDA. Based on estimated marginal means. R: removal of blood during ANH, A: addition of colloid during re-infusion of Hextend®

*The mean difference is significant at the .05 level.

Statistically significant differences were measured in EDA during the removal of blood for the initial phase of acute normovolemic hemodilution (ANH). The mean difference between Baseline and R-5% was $-1.4 \pm 0.37\text{cm}^2$ ($p < .005$). Other statistically significant differences in mean EDA were observed between baseline and R-10% ($-1.8 \pm 0.37\text{cm}^2$, $p < .001$) and baseline and R-15% ($-2.9 \pm 0.35\text{cm}^2$, $p < .001$). During the re-establishment of intravascular volume (A-10%, A-5%, final) with Hextend®, measurements of EDA were not statistically significantly different from baseline values. The EDA differences in area between baseline and A-10% were $-1.4 \pm 0.59\text{cm}^2$ ($p < .154$). No distinguishable difference in mean values was observed between baseline and A-5% ($0.03 \pm 0.508\text{cm}^2$, $p < 1.000$) and baseline and final ($0.03 \pm 0.437\text{cm}^2$, $p < 1.000$).

Likewise, differences in the measurements of mean ESA were statistically significant ($p < .0001$, Table 2). The ESA mean values, standard error and 95% confidence intervals across the 7 measured conditions are provided in Table 4.11. The initial mean baseline measurement was $5.2 \pm 0.39\text{cm}^2$. Decreases in ESA were noted

during the withdrawal of blood through R-15% ($3.7 \pm 0.26\text{cm}^2$). Increases in ESA were observed throughout the re-infusion phase of ANH with Hextend[®] from A-10% ($4.3 \pm 0.40\text{cm}^2$) through final ($4.7 \pm 0.32\text{cm}^2$).

Condition	Mean (cm^2)	Std. Error (cm^2)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	5.2	.39	4.4	6.0
R-5%	4.6	.43	3.8	5.5
R-10%	4.4	.37	3.7	5.2
A-15%	3.7	.26	3.2	4.3
A-10%	4.3	.40	3.4	5.1
A-5%	4.6	.35	3.9	5.3
Final	4.7	.32	4.0	5.3

Table 4.11. Mean, standard error, and 95% confidence intervals for ESA.

Mixed Models ANOVA was used to evaluate statistically significant mean scores among the seven conditions. Post Hoc analysis with Bonferroni pairwise comparisons was also performed for the dependent variable, ESA, to determine where in the 6 conditions a statistically significant difference among mean scores occurred when compared to the baseline measurement (Table 4.12).

Condition	Condition	Mean Difference (cm^2)	Std. Error (cm^2)	Sig. (p)	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
R-5%	Baseline	-.56	.31	.500	-1.45	.33
R-10%	Baseline	-.77(*)	.27	.049	-1.54	-.002
R-15%	Baseline	-1.5(*)	.28	< .000	-2.26	-.66
A-10%	Baseline	-.94	.41	.176	-2.11	.23
A-5%	Baseline	-.60	.30	.334	-1.46	.25
Final	Baseline	-.53	.33	.681	-1.45	.36

Table 4.12. Bonferroni Post Hoc pairwise comparisons shown for ESA. Based on estimated marginal means. R: removal of blood during ANH, A: addition of colloid during re-infusion of Hextend[®].

* The mean difference is significant at the .05 level. Based on estimated marginal means.

Statistically significant differences were demonstrated in mean area measurements of ESA during the removal of blood in 5% aliquots between baseline and R-10% ($-77 \pm$

0.27cm², $p = .049$) and baseline and R-15% ($-1.5 \pm 0.28\text{cm}^2$, $p < .0001$). End-systolic area, like EDA, did not measure any statistically significant differences in the mean area dimensions when compared to baseline values throughout intravascular volume replacement (A-10%, A-5%, Final) with Hextend[®].

The effects of graded blood removal and re-infusion with Hextend[®] on FAC were examined. The mean, standard error, and 95% confidence intervals for 2D FAC are presented in Table 4.13. Minimal differences in the mean FAC were noted with a baseline measurement of $0.63 \pm 0.20 \text{ cm}^2$ increasing to $0.66 \pm .02 \text{ cm}^2$ at R-15% and returning to a final value of $0.67 \pm .02 \text{ cm}^2$. None of these changes reached statistical significance in mean area measurements across the six conditions of blood removal and re-infusion with Hextend[®] ($p < .369$).

Condition	Mean (cm ²)	Std. Error (cm ²)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	.63	.02	.584	.667
R-5%	.64	.02	.594	.684
R-10%	.64	.02	.598	.684
R-15%	.66	.02	.617	.693
A-10%	.67	.02	.621	.712
A-5%	.67	.02	.627	.710
Final	.67	.02	.628	.704

Table 4.13. Mean, standard error, and 95% confidence intervals for FAC.

In conclusion, a statistically significant difference was demonstrated with mean EDA measurements during blood removal between baseline and R-5% through R-15% but not during re-infusion with Hextend[®]. Likewise, statistical significance was noted with mean ESA measurements during blood removal between baseline and R-10% and R-15%, but not during the re-infusion with Hextend[®]. Therefore, Null Hypothesis 1, that there will be no statistically significant differences among the mean values of LVEDA

and LVESA by two-dimensional TEE across the seven conditions of graded blood removal and replacement is rejected. With regard to FAC, the Null Hypothesis 1 cannot be disproved, as statistical significance was not demonstrated with FAC measurements across the seven conditions of graded blood removal and replacement.

Three-Dimensional Data Results

For this study, three-dimensional LV volume assessment was accomplished with the proprietary software, *fourSight*[™] (Research Arena[™], TomTec Imaging Systems, Unterschleissheim, Germany), previously described in Chapter 3. After software analysis was completed, an EDV, ESV, and EF were calculated. Figure 4.1 is an example of a completed 3D assessment.

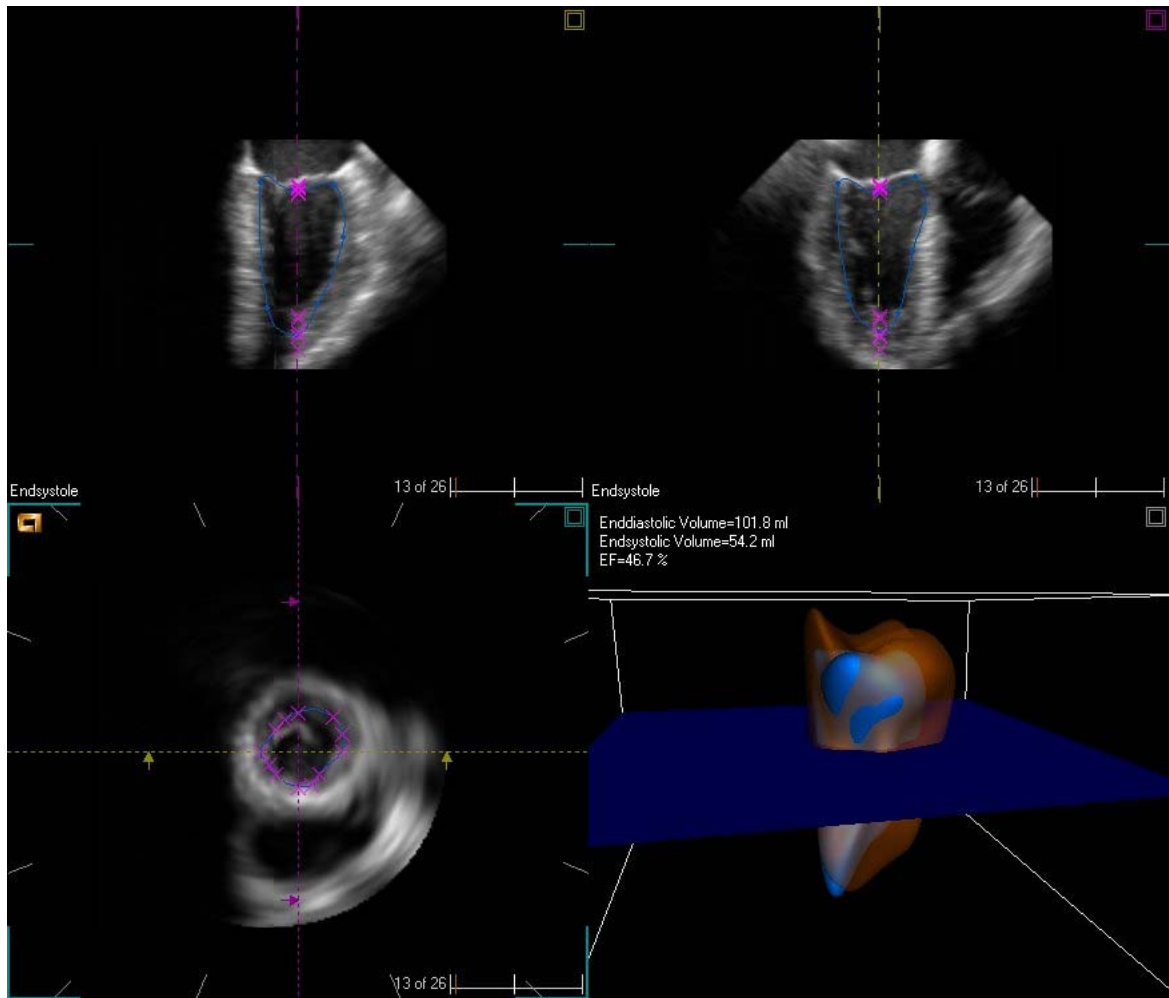


Figure 4.1. Three-dimensional LV volume assessment at baseline on Patient #21 using Research Arena™ (TomTec Imaging Systems, Unterschleissheim, Germany).

These images represent one of the three LV measurements required to obtain a 3D image for volume assessment. The two upper images of the left ventricle are orthogonal representations of one image segment, of which there were a total of 36. The LV endocardial border is traced and identified by the blue lines. The pink “X” marks the mitral valve and apex of the left ventricle. The lower left image is a cross-section of the LV chamber and guides the evaluator in the identification of the endocardial border tracing in the long axis. An outline of the LV chamber is traced with a blue line through multiple pink “X” that represents the number of 2D images evaluated and traced. The lower right image is the three-dimensional representation of the left ventricle in diastole

(red) and systole (blue). The blue cutting plane across the LV in the lower right image corresponds to the cross-sectional image in the lower left. Finally, the calculated EDV, ESV, and EF are provided in the left upper portion of the right lower 3D image. This off-line process was repeated three times for each of the seven conditions measured for each study and control patient.

Hypothesis 2 stated that there would be no statistically significant differences among the mean values of LVEDV, LVESV, and EF measurements by three-dimensional TEE across the seven conditions of graded blood removal and replacement.

Data from 29 patients were analyzed for changes in left ventricular end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF). Three-dimensional TEE measurements of EDV and EF demonstrated a statistically significant change from baseline during 5% graded hemodilution and volume replacement with Hextend[®] across the six conditions. Changes in ESV, however, did not reach statistical significance (Table 4.14).

Source	Significance (p)	F	N
EDV	< .0001	46.762	29
ESV	.427	1.039	29
EF	.002	4.807	29

Table 4.14. Tests of fixed effects reported on EDV, ESV, and EF. Significance at $p < .05$.

The EDV mean values, standard error and 95% confidence intervals across the 7 measured conditions are provided in Table 4.15. From a mean baseline measurement of $98.3 \pm 3.63\text{ml}$, gradual decreases in EDV were observed during 5% aliquots of blood removal through R-15% ($85.1 \pm 3.54\text{ml}$). During re-infusion with 5% aliquots of Hextend[®], mean EDV measurements increased from $89.2 \pm 3.44\text{ml}$ at A-10% to a final mean EDV of $110.2 \pm 4.30\text{ml}$, which was higher than the initial baseline measurement.

Condition	Mean (ml)	Std. Error (ml)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	98.3	3.63	90.9	105.8
R-5%	91.5	5.82	79.4	103.6
R-10%	88.0	3.91	80.0	96.0
R-15%	85.1	3.54	77.9	92.4
A-10%	89.2	3.44	82.2	96.3
A-5%	100.4	4.40	91.4	109.4
Final	110.2	4.30	101.4	119.0

Table 4.15. Mean, standard error, and 95% confidence intervals for EDV.

Mixed Models ANOVA was used to evaluate where a statistical significance in mean EDV values occurred. Post Hoc analysis with Bonferroni pairwise comparisons were performed to determine where in the 6 conditions a statistically significant difference among mean scores occurred when compared to the baseline measurement and these data are reported in Table 4.16.

Condition	Condition	Mean Difference (ml)	Std. Error (ml)	Sig. (p)	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
R-5%	Baseline	-6.9	4.66	.947	-20.6	6.7
R-10%	Baseline	-10.3(*)	1.96	.0001	-15.9	-4.7
R-15%	Baseline	-13.2(*)	2.22	.0001	-19.5	-6.9
A-10%	Baseline	-9.1(*)	2.81	.025	-17.4	-.86
A-5%	Baseline	2.1	3.03	1.000	-6.7	10.8
Final	Baseline	11.8(*)	2.84	.002	3.7	19.9

Table 4.16. Bonferroni Post Hoc pairwise comparisons shown for EDV. Based on estimated marginal means. R: removal of blood during ANH, A: addition of colloid during re-infusion of Hextend®.

* The mean difference is significant at the .05 level. Based on estimated marginal means.

A statistically significant difference in the mean volume measurements of EDV was discovered during the removal of 5% aliquots of blood between baseline and R-10% ($-10.3 \pm 1.96\text{ml}$, $p < .0001$) and baseline and R-15% ($-13.2 \pm 2.22\text{ml}$, $p < .0001$). Unlike one-dimensional and two-dimensional measures of left ventricular dimensions, three-dimensional EDV was able to detect statistically significant changes in the mean volume dimensions throughout most of the intravascular volume replacement with Hextend®. A

mean EDV difference was observed between baseline and A-10% ($-9.1 \pm 2.81\text{ml}$, $p = .025$) and the baseline and final measurement ($11.8 \pm 2.84\text{ ml}$, $p = .002$). Statistical significance was not found during re-infusion between Baseline and A-5% ($2.1 \pm 3.03\text{ml}$, $p = 1.000$).

Changes in three-dimensional ESV did not reach statistical significance in mean volume measurements across the six conditions when compared to baseline volume measurements ($p = .427$). The mean, standard error, and 95% confidence intervals for ESV measurements are presented in Table 4.17. From a mean baseline measurement of $39.8 \pm 2.72\text{ml}$, small changes in mean ESV were detected from baseline through R-15% ($39.3 \pm 2.19\text{ml}$). A gradual increase in mean ESV values was noted during the re-infusion phase between baseline and the final measurement ($43.2 \pm 2.87\text{ml}$).

Condition	Mean (ml)	Std. Error (ml)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	39.8	2.72	34.2	45.4
R-5%	41.1	2.40	36.2	46.1
R-10%	40.6	2.56	35.4	45.9
R-15%	39.3	2.19	34.8	43.8
A-10%	40.2	2.17	35.8	44.6
A-5%	41.9	2.96	35.8	47.9
Final	43.2	2.87	37.3	49.1

Table 4.17. Mean, standard error, and 95% confidence intervals for ESV.

The three-dimensional measurement of EF demonstrated a statistically significant difference in mean values ($p = .002$) across the seven conditions measured and are reported with their standard error and 95% confidence intervals in Table 4.18. The baseline mean EF volume was $59.9 \pm 1.94\%$. The mean R-5% value dropped to $55.9 \pm 2.04\%$ and then remained essentially unchanged during blood removal through R-15%

(54.1 ± 2.13%). An increase in mean EF values was observed from A-10% (55.6 ± 1.84%) through the final measurement of 60.1 ± 1.88%.

Condition	Mean (%)	Std. Error (%)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	59.9	1.94	56.0	63.9
R-5%	55.9	2.04	51.6	60.1
R-10%	54.4	2.04	50.3	58.6
R-15%	54.1	2.13	49.7	58.4
A-10%	55.6	1.84	51.8	59.3
A-5%	58.5	1.87	54.7	62.3
Final	60.1	1.88	56.3	64.0

Table 4.18. Mean, standard error, and 95% confidence intervals for EF.

Mixed Models ANOVA was also applied to examine the mean EF values for statistically significant differences. Post Hoc analysis with Bonferroni pairwise comparisons were performed for the dependent variable, EF, to determine where in the 6 conditions a statistically significant difference among mean scores occurred when compared to the baseline measurement. These data are reported in Table 4.19.

Condition	Condition	Mean Difference (%)	Std. Error (%)	Sig. (p)	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
R-5%	Baseline	-4.1	1.88	.259	-9.6	1.5
R-10%	Baseline	-5.5(*)	1.73	.022	-10.4	-.57
R-15%	Baseline	-5.9	2.10	.058	-11.9	.13
A-10%	Baseline	-4.4	1.68	.093	-9.2	.44
A-5%	Baseline	-1.4	1.96	1.000	-7.1	4.2
Final	Baseline	.20	1.84	1.000	-5.1	5.6

Table 4.19. Bonferroni Post Hoc pairwise comparisons shown for EF. Based on estimated marginal means. R: removal of blood during ANH, A: addition of colloid during re-infusion of Hextend®.

* The mean difference is significant at the .05 level. Based on estimated marginal means.

The Bonferroni Post Hoc pairwise analysis demonstrated one statistically significant difference in mean EF values. This mean difference of $-5.5 \pm 1.73\%$ ($p = .022$) occurred between the baseline and R-10% measurement.

In conclusion, statistical significance was detected in measurements of EDV and EF, which refute the Null Hypothesis 2, that there will be no statistically significant differences among the mean values of LVEDV and EF measurements by three-dimensional TEE across the seven conditions of graded blood removal and replacement. These data suggest that 3D measurements of EDV may detect 5% changes in blood volume when compared to 2D measurements of EDA since 3D EDV was able to detect changes during removal (R-10%, R-15%) and re-infusion (A-10%, Final). However, measurements of ESV across the seven conditions of graded blood removal and replacement did not reach statistical significance, and therefore, the null hypothesis could not be completely rejected.

Comparisons of Means between 2D and 3D Data

Hypothesis 3 stated that there would be no statistically significant differences between the mean values of two-dimensional measurements of LVEDA, LVESA, and FAC and three-dimensional measurements of LVEDV, LVESV, and EF by TEE across the seven conditions of graded blood removal and replacement. Converting the two different measures to a similar scale (i.e., percent change from baseline) is what made the comparison between the two methods in terms of left ventricular volume possible.

The paired t-test was used to compare the mean percent change from baseline between 2D and 3D measurements of EDA and EDV, ESA and ESV, and finally FAC and EF. No statistically significant differences were found between the mean percent changes from baseline when 2D EDA was compared to 3D EDV across the six post baseline conditions (Table 4.20). Erratic differences were noted among the mean values of percent change from baseline between EDA and EDV. From a mean percent difference

between EDA and EDV of $-1.1 \pm 26\%$ ($t = -.205$, $p = .839$) at R-5%, the mean percent difference at R-10% was $0.48 \pm 18.230\%$ ($t = 0.128$, $p = .900$) with a mean percent difference at R-15% measured at $-7.3 \pm 17.62\%$ ($t = 1.911$, $p = .071$). Large standard deviations were also noted between the EDA and EDV during blood removal. These erratic differences were also observed during re-infusion with Hextend® with a minimal change between A-10% ($1.9 \pm 26.28\%$, $t = .346$, $p = .773$) and A-5% ($1.9 \pm 23.64\%$, $t = .391$, $p = .700$) and an inconsistent change with the final measurement ($-6.6 \pm 20.48\%$, $t = -1.585$, $p = .127$).

Condition	Comparison	(%)	(%)	(%)	SD	SEM	95%		t-test	Sig (2-tailed) (p)
		EDA Mean	EDV Mean	Mean Diff.			Lower	Upper		
R-5%	EDA.2 - 3DEDV.2	88.0	89.1	-1.1	26.05	5.55	-12.70	10.41	-.205	.839
R-10%	EDA.3 - 3DEDV.3	89.2	88.7	.48	18.23	3.80	-7.40	8.37	.128	.900
R-15%	EDA.4 - 3DEDV.4	79.8	87.2	-7.3	17.62	3.85	-15.40	.67	-1.911	.071
A-10%	EDA.5 - 3DEDV.5	94.8	92.9	1.9	26.28	5.48	-9.47	13.26	.346	.733
A-5%	EDA.6 - 3DEDV.6	104.0	102.1	1.9	23.64	4.93	-8.30	12.15	.391	.700
Final	EDA.7 - 3DEDV.7	105.5	112.2	-6.6	20.48	4.18	-15.28	2.02	-1.585	.127

Table 4.20. Mean differences of pairwise comparisons for percent change from baseline between EDA and EDV. SD: standard deviation; SEM: standard error of the mean; CI: confidence interval; Sig: significance

The mean percent change differences from baseline between left ventricular end-systolic dimension measurements were also obtained. There were some statistically significant differences in mean percent changes from baseline between left ventricular 2D ESA and 3D ESV measurements during the removal of blood and re-infusion with Hextend® through to A-5%, with the final measurement not reaching statistical significance at the $p < .008$ level (Table 4.21).

		(%) ESA	(%) ESV	(%) Mean			95%	CI	t-test	Sig (2-tailed)
Condition	Comparison	Mean	Mean	Diff.	SD	SEM	Lower	Upper		(p)
R-5%	ESA.2 - 3DESV.2	84.1	109.2	-25.1*	33.63	7.17	-39.99	-10.16	-3.497	.002
R-10%	ESA.3 - 3DESV.3	83.6	103.4	-19.8*	29.06	6.06	-32.36	-7.22	-3.265	.004
R-15%	ESA.4 - 3DESV.4	79.2	102.7	-23.5*	35.64	7.78	-39.75	-7.31	-3.026	.007
A-10%	ESA.5 - 3DESV.5	82.7	104.8	-22.1*	24.91	5.19	-32.88	-11.33	-4.256	.000
A-5%	ESA.6 - 3DESV.6	92.4	105.2	-12.8*	26.55	5.54	-24.25	-1.28	-2.306	.031
Final	ESA.7 - 3DESV.7	99.8	111.1	-11.3	30.76	6.28	-24.26	1.72	-1.794	.086

Table 4.21. Mean differences of pairwise comparisons for percent change from baseline between ESA and ESV. SD: standard deviation; SEM: standard error of the mean; CI: confidence interval; Sig: significance; * indicates statistical significance

A statistically significant difference in the mean percent change from baseline was observed at R-5% ($-25.1 \pm 33.63\%$, $t = -3.497$, $p = .002$). A statistically significant drop to $-19.8 \pm 29.06\%$ ($t = 3.265$, $p = .004$) was noted at R-10% followed by an increased value at R-15% of $-23.5 \pm 35.64\%$ ($t = -3.026$, $p = .007$). During the re-infusion phase with Hextend[®], statistical significance was observed at A-10% ($-22.1 \pm 24.91\%$, $t = -4.256$, $p = < .0001$) and at A-5% ($-12.8 \pm 26.55\%$, $t = -2.306$, $p = .031$). No statistical significance was noted between the Final measurement and Baseline ($-11.3 \pm 30.76\%$, $t = -1.794$, $p = .086$).

Stroke volume measurements between 2D (FAC) and 3D (EF) were also examined for mean percent changes from baseline. The paired t-test was performed on the mean percent differences in stroke volume from baseline for FAC and EF and is presented in Table 4.22.

		(%) FAC	(%) EF	(%) Mean			95%	CI	t-test	Sig (2-tailed)
Condition	Comparison	Mean	Mean	Diff.	SD	SEM	Lower	Upper		(p)
R-5%	FAC.2 - 3DEF.2	103.2	92.8	10.4*	15.83	3.37	3.38	17.42	3.082	.006
R-10%	FAC.3 - 3DEF.3	105.5	92.8	12.8*	19.83	4.13	4.18	21.33	3.086	.005
R-15%	FAC.4 - 3DEF.4	105.1	92.7	12.4*	30.851	6.73	-1.64	26.44	1.841	.080
A-10%	FAC.5 - 3DEF.5	104.7	95.5	9.3*	19.68	4.10	.76	17.78	2.258	.034
A-5%	FAC.6 - 3DEF.6	107.2	102.1	5.0	18.42	3.84	-2.92	13.00	1.312	.203
Final	FAC.7 - 3DEF.7	104.3	104.1	.17	19.91	4.06	-8.24	8.58	.041	.968

Table 4.22. Mean differences of pairwise comparisons for percent change from baseline between FAC and EF. SD: standard deviation; SEM: standard error of the mean; CI: confidence interval; Sig: significance; * indicates statistical significance

Comparisons between FAC and EF revealed statistically significant differences in mean percent values during removal of blood at R-5% ($10.4 \pm 15.8\%$, $t = 3.082$, $p = .006$) and R-10% ($12.7 \pm 19.8\%$, $t = 3.086$, $p = .005$), but not at R-15% ($12.3 \pm 30.8\%$, $t = 1.841$, $p = .080$). During re-infusion phase with Hextend[®], a statistically significant mean value of $9.2 \pm 19.6\%$, $t = 2.258$, $p = .034$ was noted at A-10%. No statistical significance was observed at the A-5% ($p = .203$) or Final ($p = .968$) measurements of the re-infusion phase.

In examining Null Hypothesis 3, the comparison of end-diastolic measurements the null hypothesis was not rejected as no statistically significant changes were found between the mean percent changes from baseline when 2D EDA was compared to 3D EDV across the seven conditions. With respect to end-systolic measurements, the null hypothesis was rejected as there was a statistically significant difference in mean percent changes from baseline between left ventricular 2D ESA and 3D ESV measurements during the removal of blood and re-infusion with Hextend[®] from baseline through A-5%. The null hypothesis was also rejected with the measurements of stroke volume as statistically significant changes in mean percent values between 2D FAC and 3D EF were demonstrated during removal of blood at R-5% and R-10% and during re-infusion phase with Hextend[®] at A-10%.

Correlations between 2D and 3D Data

Hypothesis 4 stated that there would be no statistically significant correlations found between the left ventricular volume values of two-dimensional area measurements of LVEDA, LVESA, and FAC and three-dimensional volume measurements of LVEDV,

LVESV, and EF by TEE across the seven conditions of graded blood removal and replacement.

Correlations between 2D and 3D measurements of LV dimensions during graded blood removal and re-infusion with Hextend[®] were made to test Hypothesis 4. Pearson's Product Moment correlation was used to examine the correlation between EDA (2D) and EDV (3D) on the measurement of LV preload. These data are represented in Table 4.23.

	Baseline	R-5%	R-10%	R-15%	A-10%	A-5%	Final
Pearson's Correlation	.227	.110	.052	< .0001	-.012	.208	.102
Significance	.275	.602	.798	.999	.952	.391	.613
N	25	25	27	25	26	25	27

Table 4.23. Correlation of left ventricular 2D end-diastolic area (EDA) with left ventricular 3D end-diastolic volume (EDV) showing Pearson's correlation, two-tailed alpha of .05, and number of patients compared at each condition.

No statistically significant correlation was found when comparing percent change from baseline for the measurement of LV preload between EDA with EDV across the seven conditions of blood removal and replacement with Hextend[®]. Correlations ranged from a low of -.012 ($p = .952$) at R10% to .227 ($p = .275$) at baseline.

The correlations between the mean percent change from baseline of LV systolic volume for 2D (ESA) and 3D (ESV) were examined across the seven conditions of blood removal and replacement with Hextend[®]. These data from the Pearson's Product Moment correlations are presented in Table 4.24.

	Baseline	R-5%	R-10%	R-15%	A-10%	A-5%	Final
Pearson Correlation	.470	.278	.302	.478	.421	.298	.133
Significance	.018	.178	.126	.016	.032	.156	.507
N	25	25	27	25	26	25	27

Table 4.24. Correlation of left ventricular end-systolic area (ESA) with left ventricular end-systolic volume (ESV) showing Pearson's correlation, two-tailed alpha of .05, and number of patients compared at each condition.

A statistically significant correlation was detected between ESA and ESV measurements at baseline ($r = .470$, $p = .018$), R-15% ($r = .478$, $p = .016$), and A-10% ($r = .421$, $p = .032$).

The correlation between 2D FAC and 3D EF measurements of left ventricular stroke volume was examined. Person's Product Moment correlation data are reported in Table 4.25.

	Baseline	R-5%	R-10%	R-15%	A-10%	A-5%	Final
Pearson Correlation	.400	.285	.165	.356	.564	.377	.431
Significance	.048	.168	.411	.081	.003	.063	.025
N	25	25	27	25	25	25	27

Table 4.25. Correlation of left ventricular 2D fractional area change (FAC) with left ventricular 3D ejection fraction (EF) showing Pearson's correlation, two-tailed alpha of .05, and number of patients compared at each condition

A statistically significant correlation between 2D and 3D measures of stroke volume was observed at the baseline measurement ($r = .400$, $p = .048$). Statistical significance was also demonstrated during volume replacement with Hextend[®] at A-10% ($r = .564$, $p < .003$) and Final ($r = .431$, $p < .025$).

To conclude, in the measurement of preload, Null Hypothesis 4 could not be rejected as no statistically significant correlation was found when comparing percent change from baseline for the measurement of LV preload between 2D EDA with 3D EDV across the seven conditions of blood removal and replacement. Null Hypothesis 4 was rejected in the evaluation of blood removal and re-infusion with colloid when a statistically significant correlation was found between 2D ESA and 3D ESV measurements at baseline, R-15%, and A-10%. Null Hypothesis 4 was also rejected for the measurement of stroke volume between 2D FAC and 3D EF. Statistical significance

in correlation was noted between FAC and EF during volume replacement with Hextend[®] at baseline, and A-10%.

Trans-mitral Doppler Flow Data

To illustrate the changes in trans-mitral flow in this study, Figure 4.2 represents a trans-mitral pulsed wave Doppler flow image showing normal morphology of the E and A-waves in patients with normal LV function.

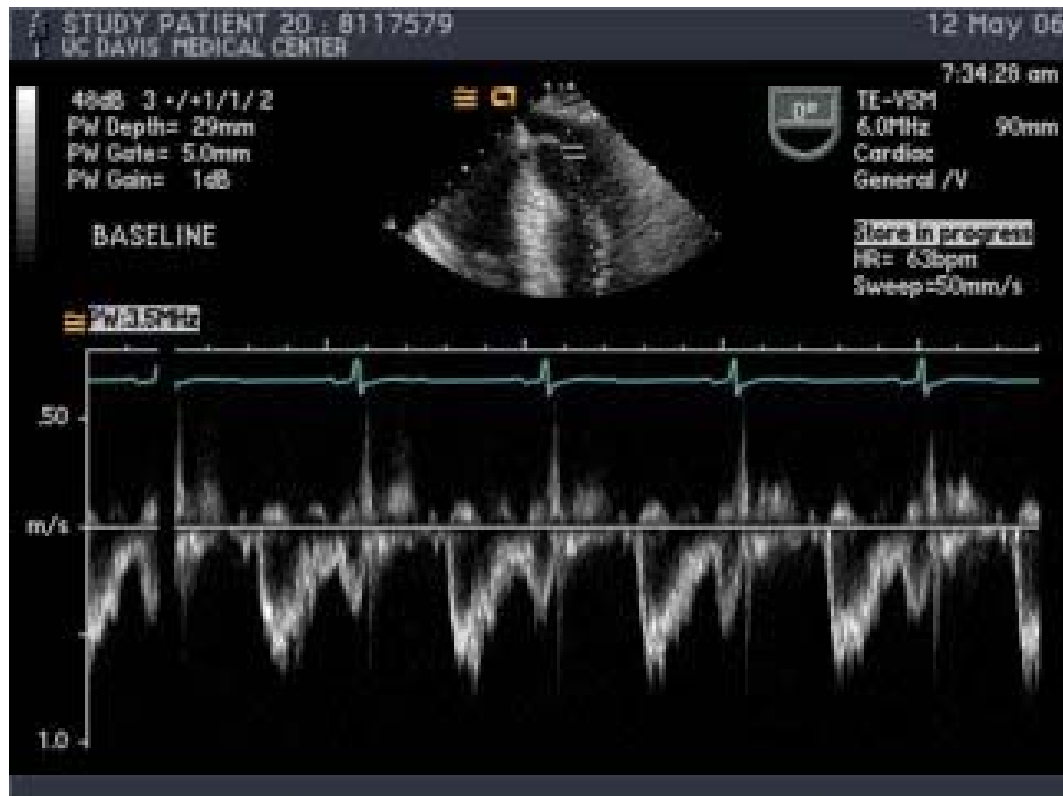


Figure 4.2. Trans-mitral Doppler flow of E and A wave velocity for Patient #20 at Baseline

The upper portion of Figure 4.2 identifies where the Doppler flow velocity is measured, which in Patient #20 is shown at the tips of the mitral valve. The prominent E-wave and smaller A-wave are shown in the bottom portion of the figure with the velocity units of measurement to the left in meters per second (m/s).

As blood was removed to a maximum of R-15%, changes were identified as the E-wave velocity decreases and the A-wave became more prominent, indicating the increased contribution of the atrial contraction (atrial “kick”) for preload (Figure 4.3).



Figure 4.3. Trans-mitral Doppler flow of E and A wave velocity for Patient #20 at R-15%

As volume was re-established with Hextend[®], there was a return to the baseline relationship of the E and A-wave ratio at the final measurement, with a decreased contribution of the atrial contraction for preload noted (Figure 4.4).



Figure 4.4. Trans-mitral Doppler flow of E and A wave velocity for Patient #20 at the Final measurement

Hypothesis 5, that there will be no statistically significant differences in TEE mean E- and A-wave values acquired by trans-mitral Doppler flow velocity measurements across the seven conditions of graded blood removal and replacement, was investigated.

To assess left ventricular function across the seven conditions of blood removal and replacement with Hextend[®], thirty-three patients were analyzed for changes in mean scores with trans-mitral Doppler flow interrogation. The various E and A wave measurements (mean \pm SD) are presented in Table 4.26(A) and the E/A wave and E_{TVI}/A_{TVI} ratios are presented in Table 4.26(B).

	Peak E (m/s)		Peak A (m/s)		Eacc (sec)		Aacc (sec)		Edec (sec)		Adec (sec)		E _{TVI} (cm)		A _{TVI} (cm)	
	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE
Baseline	.61	.02	.476	.275	106.9	4.1	76.3	3.1	153.5	10.3	114.2	8.4	.12	.01	.06	.01
R-5%	.58	.02	.431	.275	99.0	4.1	82.5	3.1	166.6	10.3	124.5	8.4	.10	.01	.06	.01
R-10%	.54	.02	.418	.275	104.0	4.1	83.7	3.1	181.2	10.3	113.9	8.4	.11	.01	.07	.01
R-5%	.54	.02	.437	.279	100.6	4.1	77.5	3.1	153.6	10.4	112.8	8.4	.11	.01	.06	.01
A-10%	.63	.02	.474	.275	102.9	4.1	81.6	3.1	170.7	10.3	132.8	8.4	.11	.01	.07	.01
A-5%	.66	.02	1.465	.275	107.9	4.1	86.2	3.1	170.8	10.3	120.6	8.4	.12	.01	.07	.01
Final	.70	.02	.540	.275	101.9	4.1	80.3	3.1	159.9	10.4	118.2	8.4	.13	.01	.07	.01

Table 4.26(A). Trans-mitral Doppler flow data sheet for E and A wave measurements. Peak E: Peak E-wave velocity; Peak A: Peak A-wave velocity; Eacc: E-wave acceleration time; Aacc: A-wave acceleration time; Edec: E-wave decoration time; Adec: A-wave decoration time; E_{TVI}: E-wave time-velocity integral; A_{TVI}: A-wave time-velocity integral; m/s: meters/second; sec: seconds; cm: centimeters; M: mean; SD: standard deviation.

	E/A Ratio		E _{TVI} /A _{TVI} Ratio	
	M	SE	M	SE
Baseline	.476	.275	1.9	.15
R-5%	.431	.275	1.8	.15
R-10%	.418	.275	2.0	.13
R-5%	.437	.279	2.1	.32
A-10%	.474	.275	1.9	.16
A-5%	.465	.275	2.0	.22
Final	.540	.275	2.1	.18

Table 4.26(B). E/A Ratio and E_{TVI}/A_{TVI} Ratio (Mean ± Standard Error)

Nine different measurements of the E and A waves were examined and their results are reported in Table 4.27.

Source	Significance (p)	F	N
Peak E-wave velocity	< .0001	13.484	33
Peak A-wave velocity	.077	1.936	33
E/A Ratio	.690	.650	33
E-acceleration time	.396	1.048	33
A-acceleration time	.114	1.739	33
E-deceleration time	.059	2.064	33
A-deceleration time	.125	1.692	33
E-time-velocity integral	.669	.676	33
A-time-velocity integral	.772	.547	32

Table 4.27. Trans-mitral Doppler flow measurements of the E and A waves for the assessment of left ventricular function across the seven conditions of blood removal and replacement with Hextend®.

Statistical significance was achieved in only one of the measured indices. Peak E-wave velocity detected a statistically significant difference ($p < .0001$) in the mean scores across the seven conditions measured and are reported with their standard error and 95% confidence intervals in Table 4.28. From a mean Baseline measurement of $.61 \pm .02$ m/s, there was a decrease in mean peak E-wave velocity measurements throughout the blood removal to a mean value of $.54 \pm .02$ m/s at R-15%. A subsequent increase in mean peak E-wave velocity values during re-infusion was observed from A-10% ($.63 \pm .02$ m/s) through the Final measurement ($.70 \pm .02$ m/s).

Condition	Mean (m/s)	Std. Error (m/s)	95% Confidence Interval	
			Lower Bound	Upper Bound
Baseline	.61	.02	.56	.66
R-5%	.58	.02	.52	.63
R-10%	.54	.02	.49	.59
R-15%	.54	.02	.48	.59
A-10%	.63	.02	.58	.69
A-5%	.66	.02	.60	.71
Final	.70	.02	.65	.76

Table 4.28. Mean, standard error, and 95% confidence intervals for peak E-wave velocity; m/s: meters per second.

The Bonferroni pairwise Post Hoc comparison was completed to determine where in the 6 conditions a statistically significant difference among peak E-wave velocity mean

scores occurred when compared to the baseline measurement. These data are reported in Table 4.29.

Condition	Condition	Mean Difference	Std. Error	Sig.	95% Confidence Interval for Difference	
					(m/s)	(m/s)
R-5%	Baseline	-.034	.024	.890	-.098	.029
R-10%	Baseline	-.070(*)	.024	.022	-.133	-.006
R-15%	Baseline	-.071(*)	.024	.020	-.135	-.007
A-10%	Baseline	.025	.024	1.000	-.039	.088
A-5%	Baseline	.048	.024	.268	-.015	.111
Final	Baseline	.095(*)	.024	.001	.031	.158

Table 4.29. Bonferroni Post Hoc pairwise comparisons shown for peak E-wave. Based on estimated marginal means. R: removal of blood during ANH, A: addition of blood during re-infusion of Hextend® * The mean difference is significant at the .05 level. Based on estimated marginal means.

Post Hoc Bonferroni pairwise comparisons of mean peak E-wave velocity measurements detected significant changes during the removal of blood between Baseline and R-10% ($-.070 \pm .024\text{m/s}$, $p = .022$) and Baseline and R-15% ($-.071 \pm .024\text{m/s}$, $p = .020$). In addition, a statistical significance was detected between the Baseline and Final mean peak E-wave velocity measurement during re-infusion with Hextend® ($.095 \pm .024\text{m/s}$, $p = .001$).

In conclusion, the Null Hypothesis 5, that there will be no statistically significant differences in TEE mean values of E- and A-wave measurements acquired by trans-mitral Doppler flow velocity across the seven conditions of graded blood removal and replacement, was not rejected with the exception of peak E-wave velocity, which demonstrated a statistically significant mean difference at R-10%, R-15%, and final ($p < .0001$).

Hemodynamic Data (Study Group)

Although not part of the hypotheses tested, hemodynamic data collected for the 33 patients studied during blood removal and replacement with Hextend® are reported for

completeness. These vital sign measurements of systolic (SBP), diastolic (DBP), mean arterial (MAP) pressures, and heart rate (HR) are presented in Table 4.30.

Condition	SBP		DBP		MAP		HR	
	(mmHg)		(mmHg)		(mmHg)		(bpm)	
	M	SE	M	SE	M	SE	M	SE
Baseline	111	2.9	60	2.0	76	2.3	71	2.2
R-5%	99	3.1	55	2.0	70	2.5	66	2.2
R-10%	102	3.6	58	2.3	72	2.8	65	2.1
R-15%	99	4.2	58	1.9	72	2.4	68	2.1
A-10%	109	4.0	61	2.2	76	2.5	67	2.2
A-5%	116	3.4	64	2.0	82	2.3	67	2.3
Final	115	4.4	61	1.8	78	2.0	66	1.8

Figure 4.30. Hemodynamic measurements (mean \pm SE) for SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, and HR: heart rate; mmHg: millimeters of mercury, bpm: beats per minute (Study Group)

Mixed models ANOVA were completed on these data and are presented in Table 4.31.

Measurement	SBP	DBP	MAP	HR
p	.001	.054	.003	.052
F	5.180	2.345	4.247	2.373

Table 4.31. Measurements of SBP, DBP, MAP, and heart rate with F statistic and p value ($p < .05$)

Mixed models ANOVA demonstrated a statistically significant difference in mean values of SBP ($p = .001$, $F = 5.180$) and MAP ($p = .003$, $F = 4.247$). Bonferroni pairwise comparisons demonstrated a statistically significant difference between the mean scores of SBP ($p = .014$) and MAP ($p = .044$) during blood removal at R-5%. No other statistically significant findings were discovered. When examining the actual changes of these two measurements, SBP demonstrated an overall difference of 17 mmHg throughout blood removal and replacement with Hextend[®] with MAP demonstrating a 12 mmHg difference. At R-5%, SBP and MAP measurements demonstrated an 11 mmHg and 6 mmHg difference from baseline, respectively. Although these findings were statistically significant, it is difficult to translate these differences into a clinically

significant discovery when the mean scores for all of these hemodynamic parameters are put into context.

Control Data to Assess Changes Over Time

Five patients undergoing elective open prostatectomy were used as controls to evaluate the effects of anesthesia over time on left ventricular chamber dimensions and function. The demographic data for these five control patients are shown in Table 4.1. After induction of general anesthesia, baseline measurements of left ventricular chamber dimensions and function were performed. The measurements were repeated twenty minutes after the baseline recordings. A final set of data was collected twenty minutes after the mid-point recording (forty minutes after baseline measurements).

The LV dimensional measurements data for 1D (cm), 2D (cm²), and 3D (ml) the control patients are presented in Table 4.32.

LV Dimension	Baseline		20 Minutes		40 Minutes	
	Mean	SE	Mean	SE	Mean	SE
1D EDD	4.2	0.2	4.5	0.2	4.5	0.1
2D EDA	12.4	1.3	12.6	1.3	13.8	1.0
3D EDV	117.0	5.8	123.5	7.4	124.1	9.1
1D ESD	2.6	0.2	2.7	0.3	2.7	0.2
2D ESA	5.3	0.8	5.8	1.2	6.3	1.0
3D ESV	45.8	2.8	57.7	4.5	56.2	5.1
1D FS	.61	2.7	53.2	2.1	54.4	3.0
2D FAC	.57	0.04	.552	0.06	.54	0.04
3D EF	60.6	2.7	53.2	2.1	54.4	3.0

Table 4.32. Mean \pm SD for 1D, 2D, and 3D LV measurements in 5 control patients.

A statistically significant difference among mean values was found with the left ventricular 1D measurement of EDD ($p < .030$, $F = 9.483$). No other left ventricular measurement techniques achieved statistically significant changes across the three conditions (Table 4.33).

Measurement	Significance	F	N
1DEDD	.030	9.483	5
1DESD	.310	1.594	5
1DFS	.982	0.018	5
2DEDA	.428	1.059	5
2DESA	.255	1.964	5
2DFAC	.617	0.546	5
3DEDV	.171	2.839	5
3DDSV	.126	3.629	5
3DEF	.055	6.563	5

Table 4.33. Mixed models ANOVA of left ventricular dimensional measurement of control patient data, $p < .05$.

A Post Hoc analysis with Bonferroni pairwise comparisons was also performed for the dependent variable, EDD, to determine where a statistically significant difference among mean values occurred when compared to the baseline measurement. These data are presented in Table 4.34.

Condition	Condition	Mean Difference (cm)	Std. Error	Sig.	95% Confidence Interval for Difference	
					Lower Bound	Upper Bound
20 minutes	Baseline	.312(*)	.072	.025	.059	.565
Final (40 min)	Baseline	.310	.212	.436	-.431	1.051

Table 4.34. Bonferroni Post Hoc pairwise comparisons shown for EDD. Based on estimated marginal means. * The mean difference is significant at the .05 level

A statistically significant difference in the EDD mean value of $.312 \pm .07$ cm was found in the measurement between Baseline and twenty minutes ($p = .025$). No significance was found between the 20-minute and the Final reading ($p = .436$).

Trans-mitral Doppler flow measurements were also obtained across the three conditions of Baseline, 20 minutes and Final (40 minutes) in the five control patients. The data means \pm SD for the E and A wave measurements are presented in Table 4.35.

	Peak E (m/s)		Peak A (m/s)		E/A Ratio		Eacc (sec)		Aacc (sec)		Edec (sec)		Adec (sec)		E _{TVI} (cm)		A _{TVI} (cm)	
	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE	M	SE
Baseline	.54	.03	.35	.02	1.5	.11	105.6	20.6	95.2	15.8	152.1	20.0	99.9	25.6	.08	.006	.05	.01
20 min.	.63	.04	.34	.03	1.8	.12	127.8	14.3	91.2	3.6	154.1	9.3	87.0	5.9	.11	.008	.04	.006
Final	.61	.10	.37	.04	1.6	.08	130.1	16.3	75.8	4.7	168.2	15.1	89.0	11.9	.11	.01	.04	.01

Table 4.35. Trans-mitral Doppler flow data sheet for E and A wave measurements. Peak E: Peak E-wave velocity; Peak A: Peak A-wave velocity; Eacc: E-wave acceleration time; Aacc: A-wave acceleration time; Edec: E-wave deceleration time; Adec: A-wave deceleration time; E_{TVI}: E-wave time-velocity integral; A_{TVI}: A-wave time-velocity integral; m/s: meters/second; sec: seconds; cm: centimeters; M: mean; SE: standard error.

The Mixed Models ANOVA was calculated to examine for statistical significance among the various measures of trans-mitral Doppler flow images of the E and A waves. No statistical significance was demonstrated in any of the measurements across the conditions analyzed. These results are presented in Table 4.36.

Measurement	Significance	F	N
Peak E-wave	.110	4.043	5
Peak A-wave	.698	0.395	5
E/A ratio	.123	3.704	5
E-acceleration time	.510	0.801	5
A-acceleration time	.082	4.971	5
E-deceleration time	.448	0.987	5
A-deceleration time	.855	0.163	5
E _{TVI}	.073	5.384	5
A _{TVI}	.811	.221.5	5

Table 4.36. Mixed models ANOVA of trans-mitral Doppler flow measurements of control patient data, $p < .05$. Peak A: Peak A-wave velocity; Eacc: E-wave acceleration time; Aacc: A-wave acceleration time; Edec: E-wave deceleration time; Adec: A-wave deceleration time; E_{TVI}: E-wave time-velocity integral; A_{TVI}: A-wave time-velocity integral.

Finally, a comparison was performed between the control and experimental groups to observe for any differences in the measured parameters of LV dimensions and function. Two measurements demonstrated statistically significant differences. The three-dimensional measurement of EDV was statistically significant between the control and experimental group ($p = .03$). In addition, the trans-mitral Doppler flow measurement of E_{TVI} demonstrated a statistically significant difference between the two groups ($p < .01$).

Table 4.37 represents the statistically significant differences between the experimental and control patients for EDV and E_{TVI} .

Group	EDV (ml)	E_{TVI} (cm)	Sig. (p)	N
Experimental	98.3 ± 3.6	0.12 ± .01	.03	29
Control	117.0 ± 5.8	0.08 ± .01	.01	5

Table 4.37. Mean ± SE differences between Study and Control patients.

From Table 4.37, a difference in EDV of 18.7 ml was detected between the study and control group. This difference was most likely due to the small number in the control group in comparison to the study group and the disparity in the standard error. The difference observed between the two groups for the trans-mitral Doppler flow measurement of E_{TVI} (.04 cm) is small and also reflect the disparity in the number of patients in each of the groups. Therefore, based on the reasons described, the detected differences observed between these two measurements were thought to be clinically insignificant.

Hemodynamic Data (Control Group)

For completion of the control data, hemodynamic measurements of blood pressure and heart rate are presented in Table 4.38. None of the measured parameters demonstrated statistically significant differences during the forty-minute observation period that assessed for the impact of anesthesia on the study results.

Measurement	SBP	DBP	MAP	HR
p	.826	.657	.414	.246
F	0.201	0.467	1.107	2.031
N	5	5	5	5

Table 4.38. Hemodynamic measurements (Control Group) of SBP: systolic blood pressure, DBP: diastolic blood pressure, MAP: mean arterial pressure, and HR: heart rate (p < .05)

Summary

In conclusion, Chapter 4 reported and characterized the results of the data collected for left ventricular volume and function analysis by TEE. For a more

comprehensive evaluation of left ventricular chamber dimension, the three methods of 1D, 2D, and 3D measurements were analyzed. In addition, trans-mitral Doppler flow interrogation was accomplished to assess left ventricular function during graded blood removal and replacement with colloid.

One-dimensional measurements demonstrated a statistically significant difference among the mean values of EDD ($p < .0001$) and ESD ($p < .0001$), but not with FS ($p = .371$) in the 33 patients studied. Both EDD and ESD detected changes in LV diameter during blood removal with ESD detecting differences between mean values during re-infusion with colloid through A-10%. Two-dimensional measurements also demonstrated statistically significant differences among mean values of EDA ($p < .0001$) and ESA ($p < .0001$), but not with FAC ($p = .369$). Like EDD, EDA detected statistically significant differences in mean values from baseline through blood removal (R-15%), while ESA detected significant changes during blood removal but not during re-infusion with colloid. These data support that both 1D and 2D measures of LV dimension in the trans-gastric short axis view are similar in the measurement of changes in preload. These data resulted in the rejection of the Null Hypothesis 1 for EDA and ESA, but not for FAC.

The off-line analysis of 3D measurements of EDV, ESV, and EF were measured in 29 patients across the seven conditions of blood removal and replacement with the colloid, Hextend[®]. These data demonstrated that EDV measured statistically significant differences in the mean values virtually throughout blood removal and re-infusion with colloid ($p < .0001$). In addition, EDV measurements actually detected an increase in preload from baseline at the final measurement of 11.9 ml ($p = .002$). The measurement of EF demonstrated a statistically significant difference in mean values at R-10% ($p =$

.002), while ESV demonstrated no significant differences ($p = .427$). These data resulted in the rejection of the Null Hypothesis 2 for EDV and EF, but not for ESV.

The Null Hypothesis 3 was not rejected when no statistically significant differences were detected between the mean values of 2D EDA and 3D EDV measurements. The Null Hypothesis 3 was rejected when differences in mean 2D ESA and 3D ESV were statistically significant throughout blood removal and replacement with Hextend[®] (with the exception of the final measurement). The mean differences between 2D FAC and 3D EF demonstrated statistically significant differences at R-5% ($P = .006$), R-10% ($P = .005$), and A-10% ($p = .034$), rejecting Null Hypothesis 3.

Correlations between the 2D and 3D LV dimensions resulted in the Null Hypothesis 4 not being rejected for the measurements between EDA and EDV. The Null Hypothesis 4 was rejected for correlations between systolic and stroke volume measurements. The measurements of ESA and ESV detected statistically significant correlations at R-15% ($p = .044$) through A-5% ($p = .007$). Likewise, there were statistically significant correlations between FAC and EF at a-10% ($p = .033$) through the final measurement ($p = .025$).

Finally, trans-mitral Doppler flow was used to interrogate changes in E and A-wave morphology and LV function in 33 patients during blood removal and re-infusion with colloid. Of the nine parameters measured, only peak E-wave velocity detected a statistically significant difference in mean values during blood removal at R-10% ($p = .022$) and R-15% ($p = .020$) and the final measurement ($p = .024$) thereby rejecting Null Hypothesis 5. All other measurement did not provide statistical significance to reject Null Hypothesis 5.

Discussion

Introduction

Trauma patients who are hemodynamically unstable require close and aggressive resuscitation. Monitoring the efforts during resuscitation is often times difficult, as the practitioners attempt to evaluate whether intravascular volume replacement to preserve cardiac output is meeting cellular oxygen demand. Since the invention of the sphygmomanometer by Scipione Riva-Ricci in 1896, monitoring technology has advanced over the years to where more invasive techniques like the central venous and pulmonary artery catheters have augmented the basic vital signs of blood pressure and pulse rate to guide resuscitative efforts in the hypovolemic trauma patient. Since its initial introduction by Swan and Ganz in 1970, the pulmonary artery catheter has been the mainstay of cardiac assessment fluid management in the critically ill (Swan et al., 1970). As discussed earlier, recent questions have arisen as to the risk-benefit of some of these invasive techniques, namely the pulmonary artery catheter (Bundgaard-Nielsen et al., 2007; Kraut et al., 1997; Leibowitz & Beilin, 1997; Polanezyk, 2001). In addition, placement of these invasive monitors may not necessarily improve patient outcome (Bundgaard-Nielsen et al., 2007; Chalfin, 1997; Connors, 1997; Connors et al., 1996). The current trend in monitoring is an approach that utilizes a more non-invasive approach to volume assessment and cardiac function. Ultrasound technology is one of those emerging methods of patient assessment.

The importance of measuring the intravascular volume to optimize oxygen delivery is dependent on examining left ventricular (LV) preload and function during resuscitation. Echocardiography provides a “window” into the heart that allows for real-time assessment of both cardiac filling and function. Two-dimensional (2D)

transesophageal echocardiography is a standard monitor in cardiac surgery. Its use is now broadening to perioperative assessment of patients who are hemodynamically unstable or those with significant myocardial disease that require additional monitoring during non-cardiac surgery (i.e., aortic surgery). The criticism of 2D TEE has centered on the fact that preload volume assessment is measured by the cross-sectional area of the left ventricle, at the level of the papillary muscles, obtained with a two dimensional image. (Gunasegaran, 2000; Otto, 2000; Poelaert, Trouerbach, De Buyzere, Everaert, & Colardyn, 1995; Troianos, 1996). A newer three-dimensional (3D) ultrasound technology is emerging that will allow the practitioner to assess the left ventricle as a 3D image. The potential advantage to this new technology is that a more accurate estimation of left ventricular volumetric analysis may be possible. Therefore, the clinical applications of 3D TEE would be significant in measuring LV preload during periods of blood loss and replacement. The aim of this study was to evaluate and compare off-line 3D left ventricular assessment to the standard 2D technology in the non-trauma patient for its potential future use in the assessment and management of volume resuscitation of the trauma patient. In addition, trans-mitral Doppler flow was also evaluated off-line to evaluate the effects of graded blood removal and colloid replacement with Hextend[®].

Study Overview

The uniqueness of this study was that a controlled human hemorrhagic model was developed by recruiting patients undergoing surgical procedures (elective open radical prostatectomy or anterior/posterior spinal fusion) that included acute normovolemic hemodilution (ANH) as part of the intraoperative strategy to reduce heterologous blood transfusion. This prospective, non-randomized experimental study investigated the use of

transesophageal echocardiography (TEE) for the assessment of left ventricular (LV) volume changes and function during graded blood removal of 5% aliquots to total 15% of the patient's total blood volume. In addition, graded re-infusion with the colloid, Hextend[®], equal to the amount of blood withdrawn, was accomplished in 5% aliquots to study the effects on LV volume changes with TEE during the re-establishment of normal intravascular volume.

For completeness, left ventricular volume measurements are presented in order of their introduction into clinical use. With enhanced 2D computer technology, early one-dimensional measurement across the left ventricle was replaced with the ability to calculate the area of the left ventricle. For the last decade of the Twentieth Century, 2D area measurement of the left ventricle was the mainstay in preload assessment. Since the turn of the century, more powerful computer software technology has led to the ability to assess the LV structures and volume with a three-dimensional image.

One-Dimensional Left Ventricular TEE Volume Analysis

Prior to the ability to calculate on-line area measurements with 2D TEE, one-dimensional assessment of LV preload was accomplished by measuring the diameter of the endocardial border with a transgastric short axis image of the left ventricle (Gunasegaran, 2000; Lake, 1990c; Otto, 2000; Troianos, 1996). One-dimensional measurements are a quick and simple method for obtaining LV dimensions and assess preload.

In the 33 patients studied, one-dimensional left ventricular EDD and ESD chamber measurements detected changes in LV blood volume ($p < .0001$, $p < .0001$, respectively). No statistically significant differences were detected in FS ($p = .371$).

Figure 5.1 represents a graphical characterization of the changes that occurred in EDD and ESD measurements across the seven measurements of blood removal and re-infusion with Hextend[®] and illustrates the changes in EDD and ESD measurements that were statistically different from baseline.

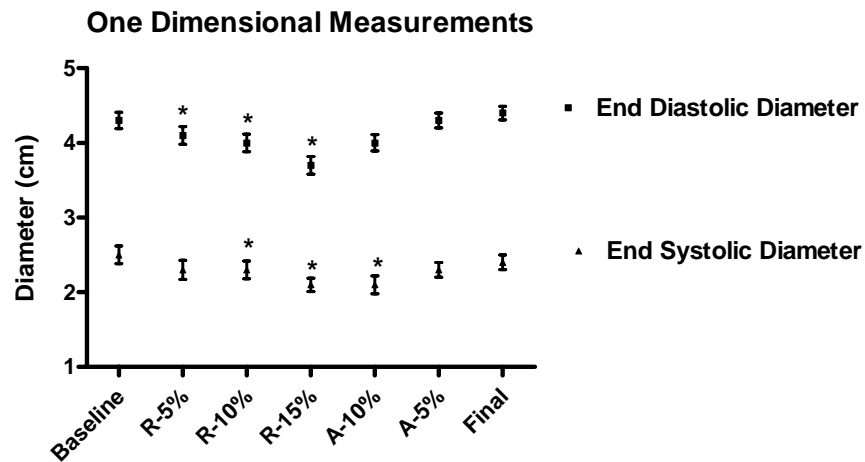


Figure 5.1. One-dimensional measurements of mean (\pm SE) for EDD and ESD
* indicates statistical significance vs. baseline ($p < .05$).

As shown in Figure 5.1, a decline in both EDD and ESD measurements was observed through R-15%. Re-infusion with the colloid, Hextend[®], demonstrated the expected increase in EDD back to baseline with a lesser increase in ESD. To emphasize these changes in EDD and ESD measurements, these data were transformed to percent change from baseline (Figure 5.2).

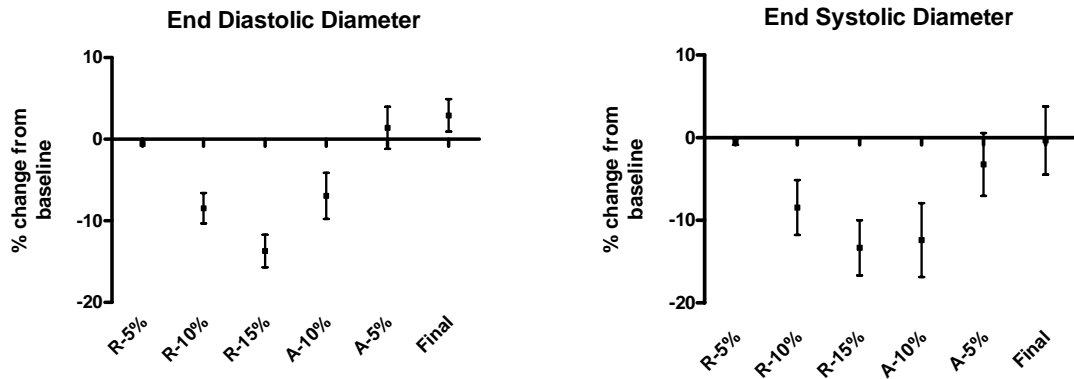


Figure 5.2. One-dimensional mean (\pm SE) measurements of EDD and ESD presented in percent changes from baseline

The changes in EDD and ESD followed their expected decrease during blood removal and increase during volume replacement with Hextend[®]. The increase observed in EDD returns to just above baseline in the final measurement, with ESD returning to baseline.

These findings are consistent with earlier work by Cheung and colleagues where LV one-dimensional data were collected but not reported (Cheung et al., 1994). In their work, the authors discussed the collection of both 1D and 2D measurements. However they decided to use 2D area measurements for the statistical comparisons stating that the 1D and 2D LV measurements were well correlated. This study by Cheung and colleagues indicates that, for rapid estimation of decreasing chamber dimensions, measurements of preload (EDD) and afterload (ESD) may provide an accurate estimation of on-going blood loss.

Fractional shortening (FS) is a one-dimensional estimation of stroke volume and its accuracy is more an approximation from ESD and ESD measurements. The advantage of FS over calculated methods of ejection fraction is that it is a simple and quick measurement to obtain. The LV measurements of diastole and systole are performed in either the m-mode or with the 2D TEE probe placed in the transgastric short axis view

that provides an image the mitral valve perpendicular to the left ventricle. For this study, the transgastric approach was used because it is the standard view used by the cardiac anesthesiologists and it produced less movement of the TEE probe during measurements. No statistical significant changes were noted in FS during blood removal and replacement with colloid underscoring the physiologic response by the heart to maintain cardiac output during small changes of 15% in blood volume.

This study indicates that during graded blood loss, 1D measurement of preload (EDD) may provide a rough estimate of whether volume resuscitation is keeping up with blood loss. There have been no previous studies examining this notion. The limitation to this method of LV measurement is that it uses a single image view, in one plane, which provides a single cavitory dimension in systole and diastole to reflect global function. It also makes the assumption that the left ventricle has normal wall motion and there is no dilated cardiomyopathy that could distort the results.

Two-Dimensional Left Ventricular TEE Volume Analysis

Two-dimensional TEE measurement is the current standard method for intraoperative LV volume assessment (Cahalan, 2004; Cheung et al., 1994; Kolev et al., 1998; Leung, 1994; Tousignant, 2000). This study examined the effect of graded blood removal and colloid replacement on the 2D measurements of EDA (preload), ESA (afterload), and by FAC, which is considered a surrogate for ejection fraction. These measurements were obtained with the TEE probe placed in the standard trans-gastric short axis view at the level of the mid-papillary muscles (Shanewise et al., 1999).

Data analysis of 33 patients demonstrated a statistically significant changes in EDA ($p < .0001$) and ESA ($p < .0001$) from baseline during 5% graded blood removal and volume replacement with Hextend[®] across the six conditions. Fractional area change,

considered a surrogate index for ejection fraction, did not reach statistical significance ($p = .369$). Figure 5.3 represents the changes observed in EDA and ESA measurements across the seven conditions of blood removal and re-infusion with Hextend[®].

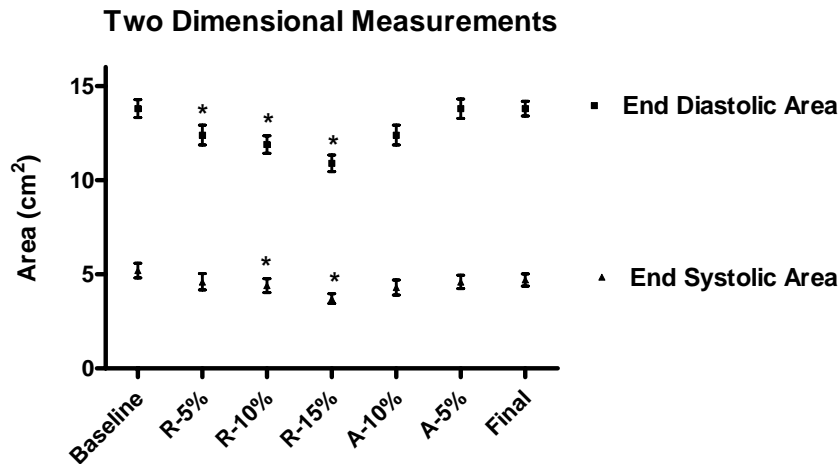


Figure 5.3. Two-dimensional mean (\pm SE) values for EDA and ESA
* indicates statistical significance ($p < 05$).

Figure 5.3 illustrates the gradual decreases in EDA, reaching statistical significance from R-5% through R-15%. These decreases were observed to a lesser extent in ESA measurements, attaining statistical significance at R-10% and R-15%. The expected increase in both measurements was seen during the re-infusion of Hextend[®]. Of note, area measurements were indistinguishable from baseline values after replacement of only 5% of the estimated blood volume.

To emphasize these changes in EDA and ESA measurements, these data were also transformed to percent change from baseline and are presented in Figure 5.4.

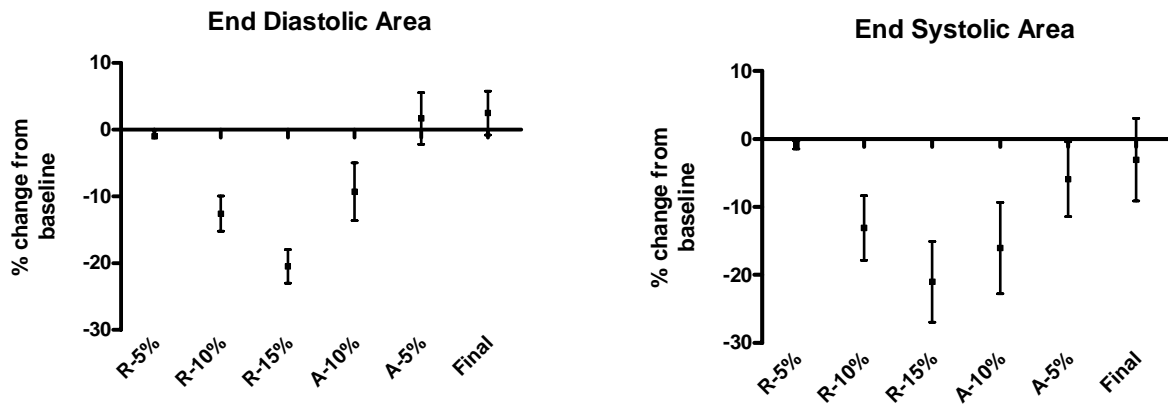


Figure 5.4. Two-dimensional mean (\pm SE) measurements of EDA and ESA presented as percent change from baseline

End-diastolic area had a difference of over 20% at R-15%, returning to 2.5% above baseline percent by the A-5% measurement. Similar changes were noted in ESA measurements throughout blood removal, nearly returning to baseline at the final measurement.

Two-dimensional EDA measurements were capable of distinguishing 5% changes in the LV chamber area dimensions during blood removal between baseline and R-5%, baseline and R-10%, and between baseline and R-15%. The differences between EDA measurements during graded blood removal are similar to those reported by Cheung and colleagues, who found statistically significant changes in LV EDA at blood removal of 2.5% aliquots in patients undergoing coronary artery bypass surgery (Cheung et al., 1994). These data for EDA are difficult to compare with those of Reich et al in their investigation of pediatric cardiac surgical patients who were subjected to 5-8% reduction in blood volume (Reich et al., 1993). Besides the differences in heart size and dimension between adult and pediatric patients, design differences make it difficult to compare their studies to this one. While Cheung's group examined differences in graded blood removal

between patients with normal and abnormal LV wall motion, Reich and associates observed the effects of graded blood removal based on systolic blood pressure changes in patients aged 6 to 36 months undergoing surgery for repair of congenital heart lesions. More importantly, neither of these investigators examined EDA during a re-infusion period nor are there any other comparable data in the literature that used this study's protocol.

In a similar design to this study, Bak and colleagues examined the effects of ANH in eight adult patients with no known cardiac disease undergoing scoliosis surgery (Bak et al., 2000). The patient's blood removal was achieved with simultaneous colloid/crystalloid re-infusion in two aliquots to a total of approximately 1400 ml, based on weight and a nomogram formula of:

$$\text{Volume Lost} = \text{blood volume} \times \ln(\text{hemoglobin}_{\text{start}}/\text{hemoglobin}_{\text{final}})$$

(\ln is the natural logarithm). Hemodilution was attained with a total volume twice that withdrawn and consisted of equal volumes of Lactated Ringers (LR) and 4% Albumin. Statistically significant differences were demonstrated in EDA as well as ESA and FAC both at the end of blood removal and re-infusion of the LR/4% Albumin mixture ($p < .05$). The current study examined smaller aliquots of blood removal and replacement than those by Bak and colleagues, and re-infusion was done separately from blood removal. By measuring these two phenomena independently and with smaller aliquots, a more accurate assessment of LV filling and function was possible. In addition, volume replacement was completed with the colloid, Hextend[®], in 5% aliquots, equal to the blood removed, which strengthened the study's design.

This study supports those of others (Brown, 2002; Cheung et al., 1994; Hanowell, 1998; Reich et al., 1993; Tousignant, 2000) that EDA as a measure of preload appears to be an effective method for assessing LV preload during periods of on-going blood loss. Decreases in EDA (preload) is an expected and well-described physiologic effect that is observed with a rapid decrease in intravascular volume similar to that which occurred during blood removal in this study (Lake, 1990a; Mohrman, 2003). From this study and those discussed above, it is reasonable to accept the utilization of EDA as a method to assess on-going intravascular volume resuscitative efforts during acute blood loss. If quantitative measurements of EDA demonstrated the stabilization of EDA during on-going blood loss, the practitioner could presume that intravascular volume was being effectively re-established. The mean EDA values presented in Table 4.9 of Chapter 4 indicated a flattening of the EDA measurements during re-infusion with Hextend[®] back to values indistinguishable from baseline. From a clinical monitoring standpoint, it is interesting that EDA returned to near baseline measurements with colloid infusion by A-5%. There are no studies in the literature available for comparison that examined both blood removal and re-infusion with colloid. Thus, further research is indicated to explore this uncertainty surrounding adequate volume replacement with colloids.

Measurements of ESA were able to detect a statistically significant difference in 5% graded blood removal between baseline and R-10% and R-15%. Similar findings regarding changes in ESA were reported by Cheung and Reich (Cheung et al., 1994; Reich et al., 1993). While Cheung and colleagues presented no numerical data, they did report a statistically significant difference in their measurements of ESA during graded blood removal. Reich and associates presented a graphical representation reporting a

statistically significant difference in ESA at a decrease in systolic blood pressure of 5 mmHg ($p < .05$) and 10 mmHg ($p < .01$) during blood removal. A decrease in the ESA was reported by both of these groups of investigators and is consistent with the findings in this study. Neither of these authors studied the effects of re-infusion on ESA. The statistically significant finding that ESA significantly decreases with graded blood removal may be expected. Systolic function can be affected by decreases in arterial blood pressure that is associated with hypovolemia, favoring a decreased afterload. The decreases in ESA during graded blood removal (hypovolemia) described in this study may be a result of reduced LV size and arterial pressure (afterload). Furthermore, ongoing blood removal under general anesthesia may have indirectly increased LV contractility by activating the sympathetic nervous system through the autonomic nervous system.

No statistically significant changes were found in FAC measurements during the graded blood removal and re-infusion. Similar results were reported by both Cheung and Reich in their study of graded blood removal in both adult and pediatric cardiac surgical patients (Cheung et al., 1994; Reich et al., 1993). This would indicate that FAC, considered a surrogate for stroke volume, remains constant during periods of changes in LV preload. These results emphasize the physiological response by the heart to maintain cardiac output during periods of decreasing intravascular volume (Boulpaep, 2003b). The human hemorrhagic model applied in this study removed 15% of the patient's total blood volume. According to the hemorrhage classifications developed by the American College of Surgeons' Committee on Trauma, a 15% loss in blood volume would constitute a Class I hemorrhage (Table 1.1) and at this level of blood loss, a patient may not exhibit

changes in hemodynamic measurements of blood pressure and heart rate. No statistically significant changes in hemodynamic parameters of blood pressure and pulse rate were identified in this study during graded blood removal and re-infusion. This work supports the concept that the effects on these hemodynamic parameters, initially used to characterize intravascular volume, cannot detect early signs of hemorrhage because subtle autonomic physiologic responses to intravascular volume loss equal to 15% preserves cardiac output in early shock in an effort to maintain oxygen delivery without overt signs in blood pressure and pulse rate (Boulpaep, 2003b; Mohrman, 2003). Finally, TEE measurements may provide critical information regarding changes in intravascular blood volume and preload in the early stages of shock that are not evident with standard vital signs.

The Null Hypothesis 1 stated that no statistically significant differences among mean values of LVEDA, LVESA, and FAC among the seven conditions of graded blood removal and replacement would be detected with 2D TEE. The null hypothesis was rejected for the measurements of LVEDA and LVESA because statistical significance was noted in these measurements during blood removal. Null Hypothesis 1 was not rejected with respect to the measurement of FAC because no statistically significant changes were detected both in graded blood removal and re-infusion with colloid. Based on previously discussed studies by Cheung and Reich, statistically significant changes might be expected in the measurements of LVEDA and LVESA during blood removal while the potential for significant changes in FAC was unknown. The uniqueness of this study allowed for the evaluation of both blood removal and replacement with colloid in a human hemorrhagic model in patients that were presumed to have normal LV function.

No previous studies examined the effects of graded blood removal using ANH in a healthy patient population. And no other study examined the re-infusion period with colloid, but it was anticipated that 2D measurements of EDA, ESA, and FAC might detect changes during this phase. This study demonstrated statistically significant changes in LVEDA and LVESA during blood removal with a return to baseline by A-5%. The fact that TEE detected a return to near baseline values at the A-5% measurement invites the notion that adequate volume replacement may actually occur with less volume when colloid is used. An increase in the oncotic pressure that resulted from the infusion of colloid is thought to be responsible for the re-establishment of intravascular volume by the A-5% measurement. The fact that this study was able to demonstrate this phenomenon during the re-infusion phase is significant. This important finding supports the current research being performed by others to help answer questions surrounding the controversy regarding optimal perioperative fluid management and is discussed in the next section (Brandstrup, Svendsen, & Engquist, 2006; Finfer et al., 2004; Schierhout & Roberts, 1998; Verheij et al., 2006).

Three-Dimensional Left Ventricular TEE Volume Analysis

There has always been speculation that three-dimensional images of the left ventricle would be more accurate than the standard two-dimensional images at detecting volume changes. Recently, advanced and more powerful computer software has made 3D imagery available in the clinical setting. It is now necessary to examine whether the newer 3D technology can actually produce a more accurate assessment of volume compared to the standard 2D measurements used over the last twenty years.

Data from 29 patients were analyzed for changes in 3D measurements of left ventricular end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF). Statistically significant differences were detected in the measurements of EDV ($p < .0001$) and EF ($p = .002$) during graded blood removal and volume replacement with Hextend[®]. End-systolic volume changes, however, did not reach statistical significance ($p = .427$).

Figure 5.5 provides a graphical characterization of the relative changes observed in EDV and ESV across the six conditions of blood removal and re-infusion with Hextend[®].

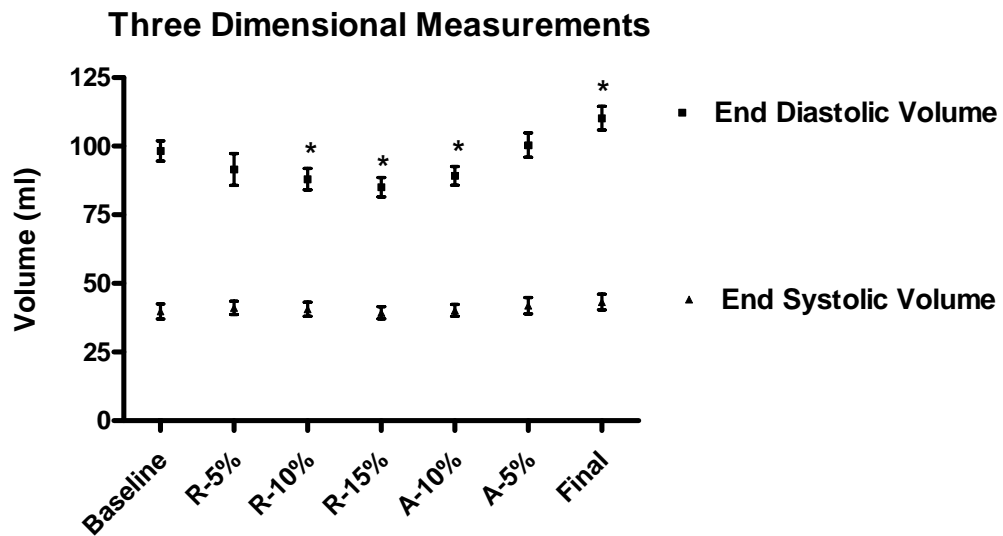


Figure 5.5. Three-dimensional mean (\pm SE) values for EDV and ESV
* indicates statistical significance ($p < .05$)

End-diastolic volume demonstrated an expected decrease during blood removal that was statistically significant from baseline at R-10% and R-15%. During this same time, ESV demonstrated minimal changes. From a physiologic standpoint, ESV may have small changes during blood removal as it attempts to maintain stroke volume. As colloid was re-infused, statistically significant differences were noted in EDV at A-10%. Baseline

volume (98.3 ± 3.63 ml) was attained by A-5% (100.4 ± 4.40 ml) with a statistically significant increase in EDV above baseline demonstrated for the final measurement (110.2 ± 4.30 ml, $p = .002$).

To emphasize these changes, percent changes from baseline measurements are presented in Figure 5.6 for EDV and ESV.

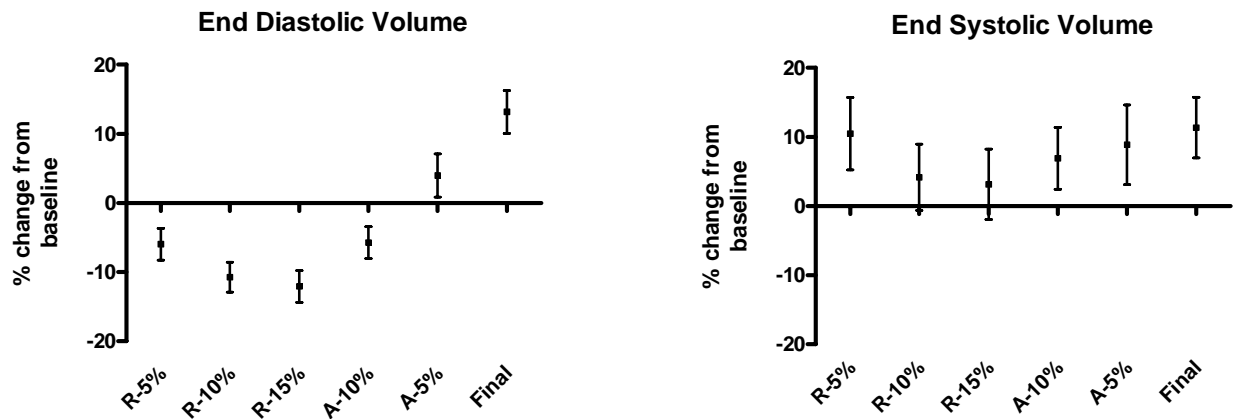


Figure 5.6. Three-dimensional mean (\pm SE) measurements of EDV and ESV presented as percent changes from baseline.

Differences in percent change from baseline were observed in EDV measurements during blood removal to approximately 12% at R-15%. As expected, increases in EDV were demonstrated throughout the re-infusion phase, with an increase in EDV of approximately 12% greater than baseline achieved at the final measurement. When these changes in EDV are translated into their actual volumetric values, the differences in preload during blood removal reach 13.2 ml less between baseline (98.3 ml) and R-15% (85.1 ml). As colloid is infused, EDV (preload) increases from the lowest value at R-15% to above the baseline measurement at A-5% (100.4 ml). From this increase in EDV of 2.1 ml, the final measurement of 110.2 ml demonstrates an increase in preload of 11.9 ml above baseline. These differences are significant when compared to ESV. There was a

small increase in the percent change from baseline with ESV measurements from approximately 10% at R-5% to 3% at R-15% during blood removal. As colloid was re-infused, values for percent change from baseline for ESV increased and returned to a R-5% value of approximately 12%. When these changes are translated into their actual volumetric values for ESV, the change is small. For example, the change in volume between R-5% and baseline for ESV is a 2.7 ml increase (41.1 ml – 39.8 ml). At R-15%, the difference from baseline is a 0.5 ml decrease (39.8 ml – 39.3 ml) with a final measurement demonstrating a 2.4 ml increase (43.2 ml – 39.8 ml) from baseline. These small changes observed in the percent change from baseline measurements of ESV support the notion that only minimal changes in ESV are observed, relative to changes in EDV, as the heart attempts to maintain cardiac output during a period of decreasing preload and stroke volume. The alterations observed in ESV measurements also provide data suggesting that ESV may require larger volume changes in EDV (preload) before subsequent changes are noted in ESV.

These findings support the notion that 3D measurements improve the capability of TEE at detecting changes in LV dimension. Both 2D and 3D TEE measurements demonstrated the ability to measure statistically significant changes in EDA and EDV, respectively during blood removal. However, 3D measurements of EDV were also capable of detecting statistically significant changes during the infusion phase with colloid. While 2D EDA measurements demonstrated a slight increase from 10.9 cm² at R-15% to 12.4 cm² at A-10%, no further increases were noted beyond A-5% (13.8 cm²). On the other hand, 3D EDV measurements were able to detect statistically significant changes from R-15% (85.1 ml) until the baseline value (98.3 ml) was exceeded at A-5%

(100.4 ml). In addition, the 3D EDV measurement detected an increase of 11.9 ml from baseline at the final measurement (110.2 ml). This finding indicates that an equal volume of colloid replacement resulted in an increase in preload from the baseline measurement. By using a unique human hemorrhagic model, this study demonstrated that 3D measurements of LV volume by TEE was capable of distinguishing 5% changes both in blood removal and replacement with colloid.

The interesting question that is posed by these results is whether a colloid, in this case, Hextend[®], can rapidly re-establish intravascular volume and preload, as measured by EDV, with less volume than the blood originally removed? Ever since the early work by Shires and colleagues in 1961 who first reported a loss in “functional fluid” (intravascular volume) with surgical trauma that was later termed “third space fluid loss” and inspired the current aggressive fluid resuscitation techniques with crystalloid, there have been spirited debates on the appropriateness of large volume resuscitation that remain unresolved (Shires, Williams, & Brown, 1961). Earlier studies that investigated differences between crystalloid and colloid for volume expansion demonstrated a higher death rate of 4% with colloids when compared to crystalloid (Schierhout & Roberts, 1998) or no difference in mortality, as was reported in the SAFE study (Finfer et al., 2004). Recently, colloid was reported to increase preload-recruitable cardiac and left ventricular stroke work indices of cardiac index and global end-diastolic volume measured by PAC through a rise in colloid osmotic pressure when compared to normal saline ($p < .001$) (Verheij et al., 2006). In addition, a recent review article by Brandstrup and colleagues of the various animal and human studies used to support the current volume resuscitation protocols used in the United States found that many of the study

designs in the animal models were questionable. Cannulation of bilateral iliac vessels causing decreased venous return from the lower extremities, the lack of biomarker standardization in human models, the differences in equilibration time for the various biomarkers, and study populations (i.e.: those with combat injuries in Vietnam) may have led to erroneous information (Brandstrup et al., 2006). These 3D EDV data may support the notion that colloid re-infusion may be more efficient at rapidly re-establishing intravascular volume. Further studies using 3D volume analysis in this area to compare colloids with the current doctrine of 3ml of crystalloid to each 1ml of blood loss are indicated and planned in future studies (Dutton, 1999; Stene, J. K., Grande, C. M., Giesecke, A, 1991).

Ejection fraction demonstrated a statistically significant difference in mean values during blood removal and re-infusion with colloid. Figure 5.7 represents the changes from baseline over the six measurements of 3D EF.

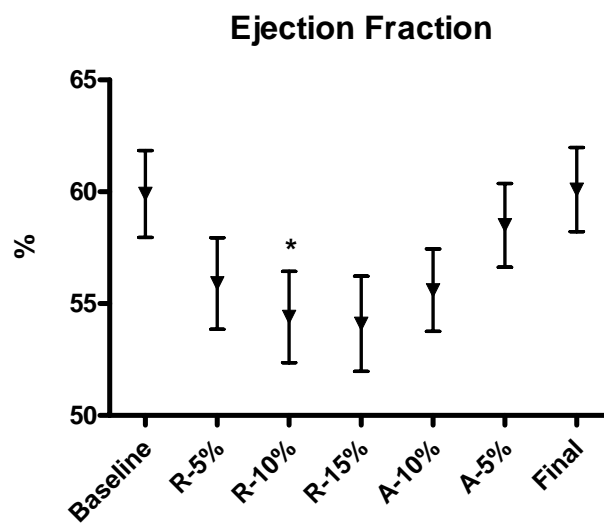


Figure 5.7. Three-dimensional mean (\pm SE) measurement of EF presented in percent changes from baseline. * indicates statistical significance ($p = .05$)

Ejection fraction demonstrated minimal changes from baseline (59.9%) through R-15% (54.1%) and during re-infusion at A-5% (55.6%) through the final measurement (60.1%). A statistically significant difference was demonstrated in the change from baseline at R-10%. These data suggest that EF was maintained during blood removal of 5% aliquots to sustain oxygen delivery to the tissues. Additionally, as intravascular volume was re-established with Hextend[®], EF returned to the baseline measurement. Although blood was removed, stroke volume variations were minimal with a difference of only 5.8% between the baseline and R-15% measurements. Ejection fraction was near normal at A-5% (58.5%) when compared to baseline. A small increase in EF was observed at the final measurement (60.1%) even though the final EDV increased by 11.9 ml. The small changes observed in the measurements of EF throughout blood removal and re-infusion with colloid support basic physiological principles of cardiac output in Class I hemorrhage, which identify no changes in normally measured vital signs of blood pressure and heart rate and underscores the ability of echocardiography to detect these subtle differences before significant hemodynamic changes are measured. This study supports the belief that replacement with colloid may rapidly re-establish intravascular volume with a lesser amount than needed when crystalloid is used. Also, it may imply that colloid replacement at 1:2 (1 ml colloid replacement to 2 ml blood loss) may be adequate, and 1:1 may be excessive.

As discussed earlier, three-dimensional LV volume analysis has only recently been made available for clinical practice. While the technology was known and described in a comprehensive review article by Gunasegaran and colleagues, the latest advancements in computer software have made real-time 3D image acquisition possible

(Gunasegaran, 2000). Only until the last year has 3D technology moved from off-line measurements of LV volume to real-time image assessment. At this time, however, real-time 3D imaging is only available with transthoracic echocardiography (TTE). Because the size of the probe is still too large for placement in to the esophagus, work is in progress to reduce the transducer size to allow for TEE real-time 3D imaging. There are studies, previously discussed in the Review of the Literature, which support the notion that 3D left ventricular assessment provides improved imaging for both structural assessment (Baweja et al., 2004; Macnab et al., 2004) and real-time volume analysis that was highly correlated to cardiac MRI: EDV $r = 0.99$, ESV $r = 0.99$, EF $r = 0.98$ (Gutierrez-Chico et al., 2005), EDV $r = 0.89$, ESV $r = 0.92$, EF $r = 0.86$ (Jacobs, 2006), EDV $r = 0.99$, ESV $r = 0.99$, EF $r = 0.98$ (Corsi et al., 2005). These studies, however, used TTE for LV analysis.

Early work with off-line 3D transesophageal echocardiography also reported highly correlated LV volume estimates ($r = 0.97$) and EF ($r = 0.95$) when compared to the gold standard of cardiac imaging (Hozumi et al., 1996; Yagi et al., 1996). Similarly high correlations were also reported by Kuhl and colleagues in their *in vitro* model in estimations of EDV ($r = 0.998$), ESV ($r = 0.996$), and EF ($r = 0.996$) (Kuhl et al., 1998).

The findings of this study are significant and add to an early body of knowledge regarding the ability of 3D TEE to assess changes in LV volume during blood removal and replacement with colloid. To date, no other studies have been published that examine the effects of 5% graded blood removal followed by 5% graded replacement with colloid on 3D TEE measurements of EDV, ESV, and EF. These data suggest that 3D TEE is capable of identifying small changes in LV volumes both during blood removal and

colloid replacement. In addition, these findings may improve the knowledge and understanding of adequate replacement with colloid to re-establish intravascular volume. These provocative findings provide an excellent opportunity for further research in the controversial area of volume resuscitation.

Comparisons of Means between 2D and 3D TEE

No statistically significant differences were found between the mean percent changes from baseline when 2D EDA was compared to 3D EDV across the seven conditions of blood removal and replacement with Hextend[®]. Erratic differences were noted among the mean values of percent change from baseline between EDA and EDV (Table 4.20). Clinical extrapolation of these comparisons must be guarded. The mean changes in the two-dimensional measurements of LV area and three-dimensional LV chamber volume demonstrated that both methods of measurements were similar throughout blood removal and colloid replacement. No previous studies in the literature have compared TEE 2D area with 3D volume measurements of LV preload. Two studies did examine 2D area and real-time 3D volume LV correlations with a transthoracic echo approach (Gutierrez-Chico et al., 2005; Jacobs, 2006). Unfortunately, the comparisons were made to cardiac magnetic resonance imaging separately and did not compare 2D with 3D. It has always been assumed that preload measurement of LV volume is more accurate with a 3D image than that obtained by a 2D representation of the left ventricle (Gunasegaran, 2000; Otto, 2000). In this study, preload measured by 3D TEE EDV detected volume changes throughout blood removal and re-infusion with Hextend[®] whereas 2D measurements of EDA detected area changes during blood removal.

The mean percent change differences from baseline between left ventricular end-systolic dimension measurements were also examined. Statistical differences were demonstrated in mean percent changes between left ventricular 2D ESA and 3D ESV measurements during the removal of blood and re-infusion with Hextend[®] from R-5% through A-5%, with the final measurement not reaching statistical significance at the $p < .05$ level (Table 4.21). This comparison of mean values between ESA and ESV may support the notion that LV systolic dimensions are easier to measure consistently because the LV chamber is small and endocardial edges are easier to detect (Otto, 2000; Troianos, 2002). More important is the consideration that both EDA and EDV demonstrated a large difference between their respective measurements at baseline that was statistically significant, which continued throughout blood removal and colloid replacement. Only the final measurement was not statistically significant because the mean differences were small. No studies in the literature were available to compare these data to other research probably because most research with TEE is directed towards analyzing preload and less interest is given to end-systolic measurements of afterload.

Stroke volume measurements between 2D FAC and 3D EF were also examined for mean percent changes from baseline during the removal of blood and re-infusion with Hextend[®]. From the data in Table 4.22, it appears that the removal of blood demonstrated statistically significant differences in mean values between FAC and EF when compared to the percent change from baseline. It is difficult to draw any conclusions from these data because, although both are a determination of stroke volume, they are acquired by different methods. As described earlier, 2D LV volume assessment is acquired with one cross-sectional image of the chamber while 3D assessment is performed after multiple 2D

images of the LV reconstructs a 3D chamber. These distinctions may have been why a statistically significant difference was demonstrated between 2D FAC and 3D EF from the first measurement that continued throughout the rest of the measurements. This may have been the reason for the statistical significance between FAC and EF. When FAC was examined independently (Table 4.13), no statistically insignificant differences were demonstrated ($p = .369$). Three-dimensional EF volume, however, did reach statistical significance ($p = .002$), but only at R-10% ($p = .022$). In addition, there was more variability in EF between the seven conditions measured.

Correlations between 2D and 3D TEE

No statistically significant correlation was found when comparing the measurement of LV preload between 2D EDA with 3D EDV across the seven conditions of blood removal and replacement with Hextend[®]. As described above, lack of correlation may have been influenced by the differences between the two methods of measurement. Two-dimensional area measurements are usually obtained in the trans-gastric short axis view at the level of the papillary muscles. This has always been the limitation of 2D echocardiography; that LV volume assessment of a three-dimensional chamber is determined with a two-dimensional measurement (Lake, 1990c; Maslow, 2003a; Otto, 2000; Tousignant, 2000; Troianos, 2002). The latest technological advancements in computer software has only recently allowed for 3D LV assessment in the clinical environment. The lack of statistical significance between EDA and EDV may underscore the early presumption that 3D actually provided a more accurate assessment of LV volume that did not correlate with 2D measurements. Both methods, however, demonstrated statistically significant changes in their respective measurements of 2D

EDA ($p < .0001$) and 3D EDV ($p < .0001$). The changes observed with 2D EDA and 3D EDV are presented in Figure 5.8A. From this graph, an expected decrease in area and volume measurements are demonstrated during blood removal with a similarly expected increase in these measurements as colloid is infused. Studies like this one are needed to further compare these two methods of LV assessment.

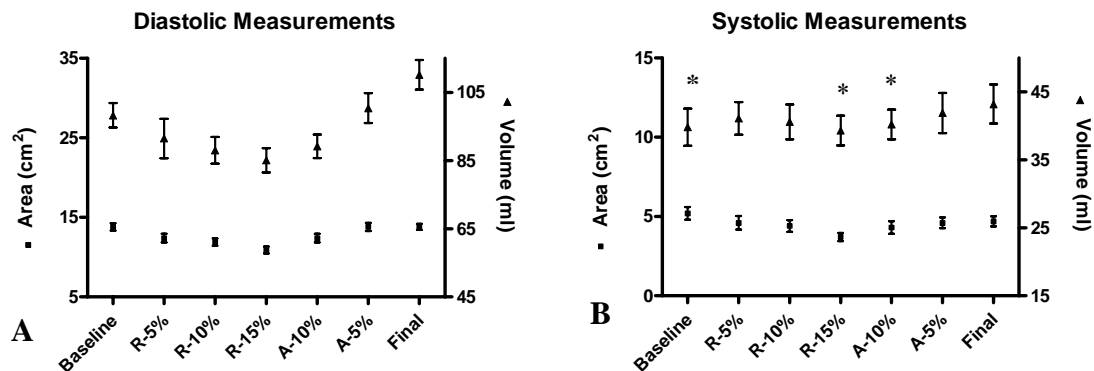


Figure 5.8. Mean (\pm SD) for correlations between two-dimensional and three-dimensional values for A: EDA and EDV, B: ESA and ESV. * indicates statistical significance

The correlations between LV systolic volume for 2D ESA and 3D ESV were also examined across the seven conditions of blood removal and replacement with Hextend[®] and are presented in Figure 5.8B. A statistically significant correlation was demonstrated between ESA and ESV measurements at baseline, R-15%, and A-10%. It is difficult to draw any clinically significant conclusions from the scattered correlations. An interesting finding was that 3D ESV demonstrated an increase at R-5% while 2D ESA decreased. This anomaly is difficult to explain, since both methods are measuring the same cavity at the same condition. At R-10%, both ESA and ESV demonstrated a decrease, but the correlation was not statistically significant. It was not until R-15% that a statistically significant correlation between ESA and ESV was noted during the blood removal phase. During colloid infusion, the two measures demonstrated increases with each 5% aliquot

that produced a weak to moderate correlation however a statistically significant correlation was only reached with the first re-infusion aliquot of A-10%. Therefore, the two measurements demonstrated an inconsistent pattern during blood removal but appeared to correlate during early re-infusion. From a physiologic standpoint, the lack of correlation during early blood loss may indicate that stroke volume was not compensated for at R-5%, demonstrated by an unexpected increase in 3D ESV not observed by 2D EDA. At R-10%, ESV demonstrated a small decrease that was also detected in ESA. As blood removal reached R-15%, and preload continued to decrease, both ESA and ESV demonstrated an expected decline. Changes in the autonomic response to this Class I hemorrhage did not appear to affect systolic volume in early blood removal (R-5%), which was demonstrated by an increase in ESV and a decrease in ESA. This contradictory change between the two measurements is difficult to describe and most likely is an anomalous finding. It is anticipated that a decrease in preload will cause an associated decrease in end-systolic dimensions. As mentioned in the previous section, systolic measurements of area and volume have not been studied to any great extent and previously discussed correlation studies did not provide useful results (Gutierrez-Chico et al., 2005; Jacobs, 2006). Using a hemorrhagic model that separated blood removal from re-infusion, this study demonstrated a correlation between 2D ESA and 3D ESV in both blood removal and replacement with colloid and a larger study is indicated to examine these effects on LV systolic dimensions.

The correlation between 2D FAC and 3D EF measurements of left ventricular stroke volume was also examined. Statistically significant correlations between 2D and 3D measures of stroke volume were demonstrated at baseline and during volume

replacement with Hextend[®] at A-10% and final. Although there was little statistically significant correlation between FAC and EF throughout blood removal and replacement with colloid, baseline and final measurements did correlate. Figure 5.9 illustrates the changes in FAC and EF over blood removal and replacement with Hextend[®].

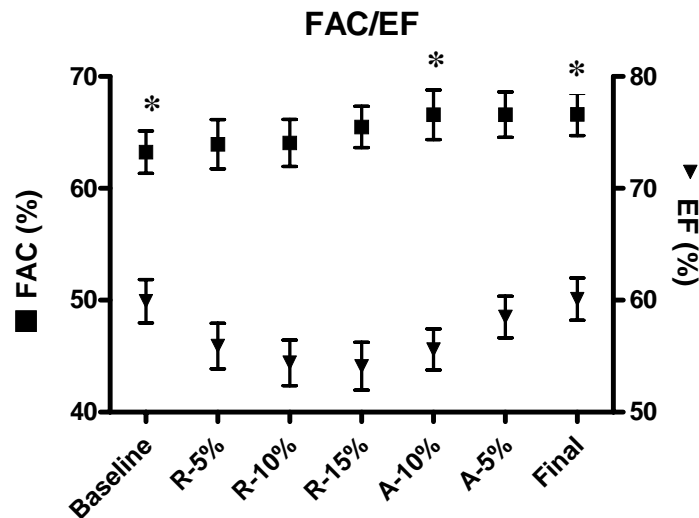


Figure 5.9. Mean (\pm SD) for correlations between two-dimensional and three-dimensional values for FAC and EF; * indicates statistical significance

When 2D FAC and 3D EF were measured independently, the changes in 2D FAC did not reach statistical significance in detecting changes across the seven conditions of blood removal and replacement with colloid ($p = .369$) while 3D EF demonstrated a statistically significant change at R-10% ($p = .022$). When the correlation between FAC and EF was performed, statistical significance was demonstrated at baseline, A-10%, and the final measurements. Figure 5.9 illustrates that only these measurements demonstrated a similar pattern of change. Measurements of FAC had minimal changes with blood removal and increased with the infusion of colloid, which essentially followed the pattern of change observed with 2D EDA and 3D ESA values (Table 5.8A and B). Two-dimensional EDA demonstrated a smaller change between measurements compared to

3D EDV. Changes in EF demonstrated decreases throughout blood removal with an increase during the re-infusion phase. While a small decrease in 2D ESA was demonstrated during blood removal, 3D ESV appeared to initially increase at R-5%, return to baseline at R-10%, and decrease at R-15%. Likewise, 2D ESA increased slightly during the re-infusion phase and appeared to flatten at A-5% and final. A more demonstrable increase was observed throughout re-infusion in the 3D ESV measurements. It was originally predicted that there would be significant correlation between FAC and EF since both are a measure of stroke volume. However, the results demonstrate minimal correlation. From a physiologic perspective, a decrease in cardiac output would be anticipated as blood volume is removed. Three-dimensional measurements of EF were able to detect approximately a 5% change in volume during blood removal while FAC remained essentially unchanged. In addition, these similar changes were detected during the colloid infusion, with a return of EF to baseline. This study demonstrates that EF detects smaller changes in blood volume compared to FAC.

Trans-mitral Doppler Flow with TEE

Trans-mitral Doppler blood flow velocity is determined by assessing the pressure gradient between the left atria and ventricle through the mitral valve. Doppler waves are emitted from the TEE probe and their frequencies are analyzed from the velocity of the red blood cells as they flow through the mitral valve. Trans-mitral Doppler flow is frequently used to assess diastolic function of the left ventricle. The E and A-wave velocities and their respective morphology can detect changes in LV compliance and help diagnose diastolic dysfunction. Trans-mitral Doppler images are quick and easy to perform, which make it ideal for immediate assessment of the left ventricle. This study

used trans-mitral Doppler flow to assess LV function during blood removal and replacement with Hextend[®].

To test Null Hypothesis 5, that there will be no statistically significant differences in TEE mean E- and A-wave values acquired by trans-mitral Doppler flow measurements across the seven conditions of graded blood removal and replacement with Hextend[®], 33 patients underwent interrogation of E- and A-wave morphology. Of the nine measurements, only peak E-wave velocity demonstrated statistically significant changes from baseline ($p < .0001$), which occurred during blood removal at R-10% ($p = .002$) and R-15% ($p = .020$) and the final measurement ($p = .001$). Figure 5.10 represents the changes in peak E-wave velocity across the seven conditions from baseline to the final measurement.

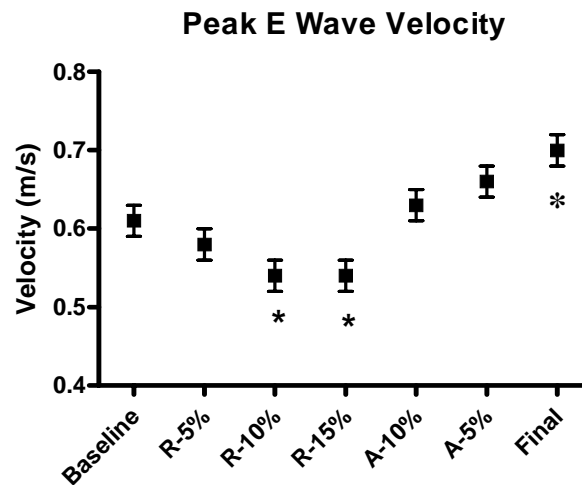


Figure 5.10. Mean (\pm SD) for peak E-wave velocity. * indicates statistical significance

The expected decrease in early filling (E-wave velocity) of the left ventricle during graded blood removal is illustrated in Figure 5.10. Early LV filling is characterized by the E-wave, and its velocity is related to the pressure gradient between the left atrium and left ventricle (Otto, 2000; Troianos, 2002). The decrease in peak E-wave velocity observed

during blood removal was the result of a reduced intravascular blood volume that was translated into a lower trans-mitral pressure gradient. As 5% aliquots of blood were removed, Peak E-wave velocity decreased at R-5% and R-10%. R-15% did not demonstrate any further decrease in peak E-wave velocity. To help support LV filling and preload, the peak A-wave velocity increased to augment LV volume, however no statistical significance was reached (Figure 4.3). As intravascular volume was re-established with colloid, the trans-mitral pressure gradient gradually increased and peak E-wave demonstrated an increased velocity. It was interesting that the peak E-wave velocity actually increased beyond baseline measurements. This phenomenon indicates that an augmentation in intravascular volume occurred beyond baseline and correlates with the findings of the 3D EDA data demonstrating that re-establishing intravascular volume with Hextend[®] may require less volume to achieve baseline measurements. As volume was re-established, peak A-wave velocity decreased, returning to baseline measurements and not reaching statistical significance during replacement (Figure 4.4).

This study found dissimilar results to those reported by Lattik and fellow researchers who studied the response to rapid intravascular infusion of 500ml of 10% pentastarch in 14 cardiac surgical patients just prior to the patients going on cardiopulmonary bypass (Lattik et al., 2002). These investigators demonstrated that E_{TVI}/A_{TVI} ratio, obtained by TEE, was predictive in assessing the responsiveness to colloid infusion. An examination of the E_{TVI}/A_{TVI} ratio data from this study did not demonstrate statistical significance. These data are illustrated in Figure 5.11.

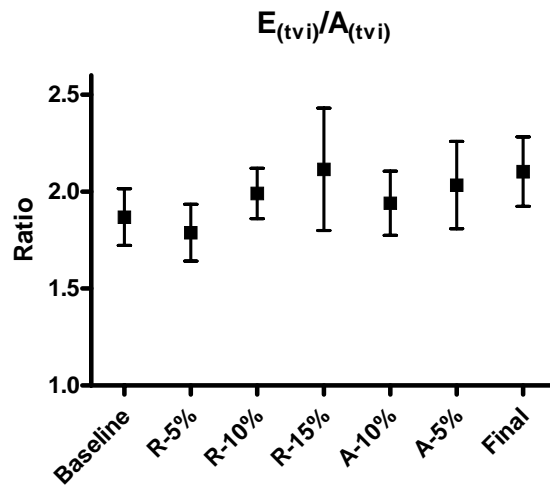


Figure 5.11. Trans-mitral Doppler flow E_{TVI}/A_{TVI} ratio.

Minimal and unpredictable changes are observed from baseline through the six measurements obtained during blood removal and replacement with colloid. It is possible that differences in the patient populations studied may have affected the results. This study was performed on patients with no known cardiac history while Lattik et al. studied patients with normal wall motion but known coronary artery disease undergoing coronary artery bypass. In addition, Lattik and coworkers used decreases in mean arterial blood pressure of 20% to 30% from the patient's baseline value as their guide to reduce blood volume whereas this study utilized predetermined volume removal and replacement. The data in this study, however, are similar to those reported by Bak and colleagues in their study of the effects of ANH on cardiac function with trans-mitral flow assessment by TEE in eight patients undergoing scoliosis repair (Bak et al., 2000). As reported earlier in this chapter with their 2D data, these researchers reported a statistically significant increase in the peak E-wave velocity of $.70 \pm 0.12$ meters per second ($p < .05$) from baseline ($.53 \pm 0.04$ m/s). No other trans-mitral indices demonstrated statistically significant differences.

Trans-mitral Doppler flow velocity was able to detect limited changes in peak E-wave velocity during blood removal to R-10% with no change occurring at R-15%. In addition, an increase in peak E-wave velocity was detected throughout colloid infusion with increases above baseline beginning at A-10%. From a physiologic standpoint, trans-mitral Doppler peak E flow demonstrated the changes in flow velocity through the mitral valve with blood removal and replacement with colloid. While these changes were interesting from a physiologic perspective, it is not a method that provides significant promise for quantitatively measuring blood loss and replacement. Therefore, its utility is limited in this capacity, however it is employed regularly for its ability to evaluate LV function and diagnose diastolic disease. The patients in this study were presumed to have normal LV function and no evidence of diastolic dysfunction was observed during data collection. It is important to keep in mind that the examination of LV diastolic function with trans-mitral Doppler flow would be important during any study where blood removal and replacement are examined so that a patient with unknown LV dysfunction will be recognized and managed appropriately.

Effects of General Anesthesia on Study Data

To examine the effects that general anesthesia may contribute to the LV measurements observed in the experimental group, five patients undergoing elective radical prostatectomy were assigned as a control population. There were no differences in demographic data between the study and control groups (Table 4.1). Of all the LV dimension and trans-mitral Doppler flow measurements taken, only the 1D measurement of EDD demonstrated a statistically significant difference between baseline and the 20-minute time interval ($p = .03$). When the mean values of EDD were examined, the

difference between the baseline (4.2 mm) and the twenty-minute interval (4.5 mm) was 0.3 mm. Therefore, when this difference was compared to the EDD measurements among the five control patients, it was considered to be clinically insignificant.

When the baseline control group data for LV dimensions and trans-mitral Doppler flow were compared to the baseline study group, statistically significant differences were demonstrated in two measurements. The three-dimensional measurement of EDV in the control patients was statistically significantly different from the study group ($p = .03$), with a difference in EDV of 18.7 ml being detected between the two groups. A review of the raw data for baseline EDV in the study group revealed measurements ranging from 137.8 ml to 64.7 ml. Given this wide range in EDV for the 33 patients in the study group, and the disparity in the standard error between the two groups (study ± 3.6 ; control ± 5.8), this difference was likely due to the small number in the control group with large baseline end-diastolic volumes in comparison to the study group. The baseline trans-mitral Doppler flow measurement of E_{TVI} demonstrated a statistically significant difference between control and study groups ($p = .01$). The difference observed between the two groups for the trans-mitral Doppler flow measurement of E_{TVI} (.04 cm) was small and also may have reflected the disparity in the number of patients in each of the groups compared to the treatment group. It is doubtful that these two statistically significant findings have any clinically significant impact and indicates that the effects of the anesthetic administered during the study did not significantly influence the measurements obtained in the study group.

Limitations to the Utility of Intraoperative TEE

Transesophageal echocardiography is limited by certain clinical conditions that could increase the likelihood of morbidity associated with its use. Any esophageal pathology such as esophageal varices, stricture, or diverticulae is an absolute contraindication to TEE use. In addition, surgical repair of a hiatal hernia or esophageal reconstruction make TEE contraindicated. These conditions could cause perforation or damage to the esophagus and cardiac sphincter with insertion of the TEE probe.

Intraoperative TEE use is also limited by patient positioning for their surgical procedure. Two consequences can occur as a result of attempting to use TEE in patients positioned other than supine. The first, and most important, is patient injury. For example, placing a TEE probe in a patient in the prone position can result in laryngeal injury. The second sequelae that can occur with intraoperative TEE is poor image quality in patients placed in positions other than supine. In this study, poor image quality was experienced in patients undergoing robotic-assisted prostatectomy. In order to enhance visualization of the operative field, steep Trendelenburg was required. This position made it difficult to acquire satisfactory images for analysis. From a physiologic standpoint, patients placed in the steep Trendelenburg position have a noticeable increase in peak inspiratory ventilation pressures and a decrease in functional residual capacity (FRC) and lung compliance. The mechanism of action for these physiologic changes is due to the movement of the abdominal contents cephalad against the diaphragm, causing the diaphragm to not only contract to ventilate the lungs but also become responsible for lifting the abdominal contents out of the thorax (Benumof, 1994). Because of poor image

quality and the confounding physiologic effects brought on with steep Trendelenburg, these patients were eliminated from recruitment.

Similar situations were encountered with those patients undergoing anterior/posterior fusions. For this procedure, the patient was placed in the right semi-lateral position. This position occasionally caused the images obtained in both the mid-esophageal and trans-gastric views to be less than optimal. However, when clear images were obtained in either of the patient populations studied, excellent 3D reconstruction and analysis was possible.

Logistical Limitations to the Study

Because of licensing issues with the manufacturer of the software, it was not until near the end of data collection that the off-line 3D analysis was initiated. The significance of this situation was that the data collection was near the end when it was realized that image optimization was best achieved with the four-chamber view centered on the monitor. Although the images obtained were acceptable for analysis, it was later appreciated how optimizing the cardiac images during acquisition was especially important for 3D analysis.

Impact of Anesthetic Management on the Study

Every attempt was made to control for the effects of anesthesia on the results obtained during the study portion of the patient's surgical procedure. To minimize the variance among anesthesia providers, two nurse anesthetists and two anesthesiologists were invited to provide the anesthetic management of the patient based on the established protocol discussed in the Methods section. The protocol provided those managing the anesthetic with a stepwise instruction of the medications to be used and the dose range to

be administered. On the day of the study, one of the two providers from the nurse and physician anesthesia staff was assigned to the operating room where the surgical procedure was scheduled. The continuity between anesthetic management was made possible because of this small working group.

Anesthetic techniques were also standardized by the study protocol. For example, while intrathecal morphine was used for postoperative pain, no local anesthetic was added. The pharmacologic sympathectomy that is associated with the use of local anesthetics in the subarachnoid space would have caused hypotension during the data collection phase when blood was being removed. This effect would have confounded the results and it would have been difficult to assess if hypotension was from the anesthetic or blood removal. Minimal deviation from the protocol was experienced during the study.

Conclusion and Future Research

The use of patients undergoing intraoperative acute normovolemic hemodilution (ANH) as part of the strategy for blood conservation provided a unique hemorrhagic model that has not been used in this capacity before. Patients underwent a controlled, graded hemorrhage equal to 15% of their total estimated blood volume, which is equivalent to a Class I hemorrhage by the Advanced Trauma Life Support guideline established by the American College of Surgeons. This study protocol had the option of re-establishing intravascular volume after blood removal with either crystalloid or colloid. The colloid, Hextend[®], a large molecular weight hetastarch, was decided upon because of the current trend in the literature suggesting that lower volume resuscitation may optimize patient outcome (Brandstrup et al., 2006; Verheij et al., 2006). An interesting finding from the three-dimensional data was that the EDV actually increased

from baseline with the infusion of Hextend[®], in equal volume to the blood removed (Baseline = 98.3±3.6ml; Final = 110.2 ± 4.3 ml). These early data may indicate that volume resuscitation with colloid may actually increase preload rapidly by its oncotic effect in drawing interstitial fluid into the intravascular space. Future studies are indicated to compare the effects of colloid to crystalloid re-infusion on LV preload in this hemorrhagic model.

Two-dimensional TEE will continue to be the mainstay for intraoperative cardiac assessment. It can provide important information regarding cardiac preload status and function in a variety of clinical settings from the patient with myocardial disease to the hypovolemic patient who is not responsive to volume boluses in the OR and intensive care setting. It was demonstrated that both 1D and 2D assessment of preload are similar for the detection of changes in EDA and EDD, respectively during blood removal. These data have been established by others (Cahalan, 2004; Cheung et al., 1994; Hanowell, 1998; Reich et al., 1993).

Three-dimensional EDV assessment of preload was able to demonstrate statistically significant changes in intravascular volume both during blood removal and re-infusion with colloid. This was not the case with the corresponding measures of preload with 2D EDA and 1D EDD. Currently, real-time 3D image acquisition is only possible with the transthoracic approach. When a transesophageal probe is developed that allows for real-time 3D assessment, this method could have considerable advantages over 1D and 2D measure of preload in that it can better guide volume replacement during the re-establishment of intravascular volume. This is especially helpful in patients who may not tolerate the rapid infusion of large quantities of fluid, namely those patients with or

the potential for cardiac failure. The use of 3D TEE volume analysis may be particularly helpful during volume resuscitation in the elderly trauma patient.

Trans-mitral Doppler flow was shown to detect volume changes with alterations in peak E-wave velocity. It is not expected that this measurement would be clinically useful for LV assessment during rapid intravascular volume changes. Trans-mitral Doppler interrogation is useful for the detection of LV diastolic dysfunction and could be helpful in diagnosing heart failure in the trauma patient and identify patients who might benefit from closer monitoring (i.e.: the elderly trauma patient).

In conclusion, from this study, questions regarding preload assessment with TEE during blood removal and replacement with Hextend[®] have been examined, but create a need for further elucidation. Future research will be directed in the area of noninvasive methods for the assessment of volume status with this hemorrhagic model. A study is planned to examine the differences between crystalloid and colloid volume resuscitation. The further evaluation of real-time 3D will occur with the availability of an appropriate probe, once it is developed.

The advancement of nursing science in the area of noninvasive monitoring is important to optimize patient care and safety. As ultrasound technology advances, it is only a matter of time before methods such as echocardiography become a standard in patient care for the evaluation and management of the critically ill. A new paradigm in patient care monitoring was established when nurses began to train in and incorporate pulmonary artery catheters as part of their routine assessment of cardiac function in the critically ill ICU patient. Now this once standard in monitoring is being questioned because of its impact on patient morbidity and mortality. A more non-invasive approach

is the new mantra in patient monitoring. Ultrasound-guided surgical procedures have been developing in areas such as gastroenterology and general surgery for such procedures as tumor biopsy. Nurses are now using ultrasound for percutaneous intravenous central catheter (PICC) line placement and for the estimation of bladder volume. More specifically, nurse anesthetists have now incorporated ultrasound technology for the routine placement of central venous access and arterial lines in the morbidly obese. In addition, with the advocacy of a multi-modal approach to pain management, anesthesia practitioners are now utilizing ultrasound-guided needle positioning for the placement of peripheral nerve blocks in the femoral and interscalene regions of the body. Therefore, as ultrasound and computer technology improve, non-invasive monitoring will become the new paradigm in the nursing care of the critically ill patient and part of that care will include echocardiography for the assessment of cardiac volume and function.

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Appendix 1

Glossary of Terms

Automated Border Detection (Acoustic Quantification): An automated method of obtaining real-time measurements of left ventricular end-diastolic area, end-systolic area, and fractional area change by computer software that detects the endocardial borders of the left ventricular cavity during the cardiac cycle.

Central Venous Pressure (CVP): The pressure within the superior vena cava. Reflects the pressure under which blood is returned to the right atrium.

Doppler Flow: The backscatter of ultrasound from moving objects (i.e.: red blood cells) create a change in a transmitted frequency depending on whether the objects are moving towards the transducer (higher frequency) or away from the transducer (lower frequency). This technique is used for determining the blood flow velocity through a valve that is between two chambers in the heart. Usually determines flow between the right atrium and ventricle (tricuspid valve), the left atrium and ventricle (mitral valve), or the left ventricle and the aorta (aortic valve).

Ejection Fraction (EF): The proportion of the diastolic volume (ml) ejected during ventricular contraction.

$$\text{LVEF} = \frac{\text{LVEDV} - \text{LVESV}}{\text{LVEDV}} \times 100$$

Fractional Area Change (FAC): The proportional change (cm²) in left ventricular area between diastole and systole.

$$\text{LVFAC} = \frac{\text{LVEDA} - \text{LVESA}}{\text{LVEDA}} \times 100$$

Fractional Shortening (FS): The simplest technique commonly used to measure the percentage of change in left ventricular dimensions (cm) between systole and diastole.

$$\text{LVFS} = \frac{\text{LVEDD} - \text{LVESD}}{\text{LVEDD}} \times 100$$

Hematocrit: The volume of erythrocytes (red blood cells) packed by centrifugation in a given volume of blood; expressed as a percentage of total blood volume that consists of erythrocytes or as the volume in cubic centimeters that result from centrifugation.

Left ventricular end diastolic area (LVEDA): The dimension of the left ventricle at the end of diastole.

Left ventricular end systolic area (LVESA): The dimension of the left ventricle at the end of systole.

Mean arterial pressure (MAP): The average arterial pressure in the artery. Can be calculated as:

$$\text{MAP} = \text{Diastolic BP} + \frac{(\text{Systolic BP} - \text{Diastolic BP})}{3}$$

Pulmonary artery occlusive pressure (PAOP): Also known as pulmonary artery wedge pressure (PAWP). The pressure measured within the pulmonary artery with the balloon at the tip of the pulmonary artery catheter inflated. Because there are no valves present in the pulmonary and the left atrium, the pressure measurement reflects left atrial pressure, which is an indication of left ventricular end diastolic pressure (in the absence of mitral valve pathology).

Preload: In cardiac physiology, the end-diastolic stretch of the muscle fiber and is approximately equal to the end-diastolic volume or pressure.

Transesophageal Echocardiography (TEE): A relatively noninvasive diagnostic method that uses ultrasound to visualize cardiac structures. With the TEE probe placed in the esophagus, all of the cardiac valves can be visualized, the dimensions of the cardiac chambers measured, and overall cardiac function analyzed.

Trans-mitral Doppler flow: see Doppler flow.

Velocity-Time Integral (VTI): Calculated as the integral of the Doppler velocity curve (cm/s) over time(s); expressed as centimeters.

Category I indications: Supported by the strongest evidence or expert opinion; TEE is frequently useful in improving clinical outcomes in these settings and is often indicated, depending on individual circumstances (e.g., patient risk and practice setting; see fig. 1).

- Intraoperative evaluation of acute, persistent, and life-threatening hemodynamic disturbances in which ventricular function and its determinants are uncertain and have not responded to treatment
- Intraoperative use in valve repair
- Intraoperative use in congenital heart surgery for most lesions requiring cardiopulmonary bypass
- Intraoperative use in repair of hypertrophic obstructive cardiomyopathy
- Intraoperative use for endocarditis when preoperative testing was inadequate or extension of infection to perivalvular tissue is suspected
- Preoperative use in unstable patients with suspected thoracic aortic aneurysms, dissection, or disruption who need to be evaluated quickly
- Intraoperative assessment of aortic valve function in repair of aortic dissections with possible aortic valve involvement
- Intraoperative evaluation of pericardial window procedures
- Use in intensive care unit for unstable patients with unexplained hemodynamic disturbances, suspected valve disease, or thromboembolic problems (if other tests or monitoring techniques have not confirmed the diagnosis or patients are too unstable to undergo other tests)

Category II indications: Supported by weaker evidence and expert consensus; TEE may be useful in improving clinical outcomes in these settings, depending on individual circumstances, but appropriate indications are less certain.

- Perioperative use in patients with increased risk of myocardial ischemia or infarction
- Perioperative use in patients with increased risk of hemodynamic disturbances
- Intraoperative assessment of valve replacement
- Intraoperative assessment of repair of cardiac aneurysms
- Intraoperative evaluation of removal of cardiac tumors
- Intraoperative detection of foreign bodies
- Intraoperative detection of air emboli during cardiectomy, heart transplant operations, and upright neurosurgical procedures
- Intraoperative use during intracardiac thrombectomy
- Intraoperative use during pulmonary embolectomy
- Intraoperative use for suspected cardiac trauma
- Preoperative assessment of patients with suspected acute thoracic aortic dissections, aneurysms, or disruption
- Intraoperative use during repair of thoracic aortic dissections without suspected aortic valve involvement
- Intraoperative detection of aortic atheromatous disease or other sources of aortic emboli
- Intraoperative evaluation of pericardiectomy, pericardial effusions or evaluation of pericardial surgery
- Intraoperative evaluation of anastomotic sites during heart and/or lung transplantation
- Monitoring placement and function of assist devices

Category III indications: Little current scientific or expert support; TEE is infrequently useful in improving clinical outcomes in these settings, and appropriate indications are uncertain.

- Intraoperative evaluation of myocardial perfusion, coronary artery anatomy, or graft patency
- Intraoperative use during repair of cardiomyopathies other than hypertrophic obstructive cardiomyopathy
- Intraoperative use for uncomplicated endocarditis during noncardiac surgery
- Intraoperative monitoring for emboli during orthopedic procedures
- Intraoperative assessment of repair of thoracic aortic injuries
- Intraoperative use for uncomplicated pericarditis
- Intraoperative evaluation of pleuropulmonary diseases
- Monitoring placement of intraaortic balloon pumps, automatic implantable cardiac defibrillators, or pulmonary artery catheters
- Intraoperative monitoring of cardioplegia administration

Appendix 2. Indications for perioperative transesophageal echocardiography by category. From Tys DM et al, Practice Guidelines for Perioperative Transesophageal Echocardiography, 1996, p. 988, with permission

Basic training

Cognitive skills

1. Knowledge of the physical principles of echocardiographic image formation and blood velocity measurement
2. Knowledge of the operation of ultrasonographs, including all controls that affect the quality of data displayed
3. Knowledge of the equipment handling, infection control, and electrical safety associated with the techniques of perioperative echocardiography
4. Knowledge of the indications, contraindications, and potential complications for perioperative echocardiography
5. Knowledge of the appropriate alternative diagnostic techniques
6. Knowledge of the normal tomographic anatomy as revealed by perioperative echocardiographic techniques
7. Knowledge of commonly encountered blood flow velocity profiles as measured by Doppler echocardiography
8. Knowledge of the echocardiographic manifestations of native valvular lesions and dysfunction
9. Knowledge of the echocardiographic manifestations of cardiac masses, thrombi, cardiomyopathies, pericardial effusions, and lesions of the great vessels
10. Detailed knowledge of the echocardiographic presentations of myocardial ischemia and infarction
11. Detailed knowledge of the echocardiographic presentations of normal and abnormal ventricular function
12. Detailed knowledge of the echocardiographic presentations of air embolization

Technical skills

1. Ability to operate ultrasonographs including the primary controls affecting the quality of the displayed data
2. Ability to insert a TEE probe safely in the anesthetized, tracheally intubated patient
3. Ability to perform a comprehensive TEE examination and differentiate normal from markedly abnormal cardiac structures and function
4. Ability to recognize marked changes in segmental ventricular contraction indicative of myocardial ischemia or infarction
5. Ability to recognize marked changes in global ventricular filling and ejection
6. Ability to recognize air embolization
7. Ability to recognize gross valvular lesions and dysfunction
8. Ability to recognize large intracardiac masses and thrombi
9. Ability to detect large pericardial effusions
10. Ability to recognize common echocardiographic artifacts
11. Ability to communicate echocardiographic results effectively to healthcare professionals, the medical record, and patients
12. Ability to recognize complications of perioperative echocardiography

Advanced training

Cognitive skills

1. All the cognitive skills defined under basic training
2. Detailed knowledge of the principles and methodologies of qualitative and quantitative echocardiography
3. Detailed knowledge of native and prosthetic valvular function, including valvular lesions and dysfunction
4. Knowledge of congenital heart disease (if congenital practice is planned, then this knowledge must be detailed)
5. Detailed knowledge of all other diseases of the heart and great vessels that is relevant in the perioperative period (if pediatric practice is planned, then this knowledge may be more general than detailed)
6. Detailed knowledge of the techniques, advantages, disadvantages, and potential complications of commonly used cardiac surgical procedures for treatment of acquired and congenital heart disease
7. Detailed knowledge of other diagnostic methods appropriate for correlation with perioperative echocardiography

Technical skills

1. All the technical skills defined under basic training
2. Ability to acquire or direct the acquisition of all necessary echocardiographic data, including epicardial and epi-aortic imaging
3. Ability to recognize subtle changes in segmental ventricular contraction indicative of myocardial ischemia or infarction
4. Ability to quantify systolic and diastolic ventricular function and to estimate other relevant hemodynamic parameters
5. Ability to quantify normal and abnormal native and prosthetic valvular function
6. Ability to assess the appropriateness of cardiac surgical plans
7. Ability to identify inadequacies in cardiac surgical interventions and the underlying reasons for the inadequacies
8. Ability to aid in clinical decision making in the operating room

Appendix 3. Recommended training objectives for basic and advanced perioperative echocardiography. From Cahalan MK et al, American Society of Echocardiography and Society of Cardiovascular Anesthesiologist Task Force Guidelines for Training in Perioperative Echocardiography, 2002, p. 649, with permission.

Appendix 4

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ACUTE NORMOVOLEMIC HEMODILUTION

I. PURPOSE

Acute normovolemic hemodilution has as its goal the conservation of blood products and the reduction in patient exposure to blood products in patients undergoing major surgical procedures with a high probability of blood loss. Acute normovolemic hemodilution accomplishes this by phlebotomy of 1-2 units, or more, of autologous blood into standard blood collection bags immediately prior to surgery and reinfusion of those products prior to completion of surgery.

II. PROCEDURE

A. Patient Selection

1. Patients undergoing major elective surgery who have an anticipated blood loss of 20% of blood volume or need for at least one unit of allogeneic, directed or autologous blood.
2. Patients that would be considered for preoperative autologous blood donation, i.e., Hct 33% or greater.
3. Patients will be given a summary of the risk/benefit evaluation and informed consent is required.
4. Contraindications to ANH include coronary artery disease, pulmonary emphysema, obstructive lung disease, anemia, severe renal disease or severe liver disease.

B. Blood Collection

1. The blood collection site will be prepared by cleansing the skin with standard aseptic technique. Blood can be collected from central vein, peripheral vein or peripheral artery.
2. Blood collection must be done by aseptic methods using sterile, pyrogen free IV lines and equipment.
3. Blood will be drawn into a standard blood collection bag containing CPDA-1 anticoagulant solution suitable for collection of 300 - 495 ml of blood.

Peripheral vein

The IV catheter should be preferably set up with 14-16 gauge needle.

Central vein

Single lumen or multiple lumen central venous catheter may be used.

Peripheral artery

O₂ saturation monitored from ipsilateral fingers

Ensure all air bubbles removed before flushing the arterial line.

4. Blood units will be agitated gently during collection to ensure adequate mixing with the anticoagulant.

5. The amount of blood collected into each bag will be monitored by checking its weight. The units should weigh from 318 g – 520 g (blood weighs 1.06 g/ml) plus the baseline measurement of the bag and anticoagulant

C. Specimen Handling, Labeling and Storage

1. Blood obtained perioperatively shall not be transfused to other patients.

2. The blood collected will be labeled with the patient's first and last name, hospital identification number, date and time of initial collection and the statement, "For Autologous Use Only".

3. Blood may be stored at room temperature for up to 8 hours or refrigerated at 1-6C up to 24 hours provided that storage at 1-6C is begun within 8 hours of initiating the collection.

D. Monitoring of Hemodilution (Anesthesia)

1. Infusion of replacement crystalloid or colloid fluids can be monitored by standard monitors (heart rate, blood pressure, O₂ sat, EKG), central venous pressure if present and volume of blood recovered.

2. Patient ANH should be drawn before and after.

3. Blood collection shall cease when the target Hct is achieved.

E. Reinfusion

Reinfusion of the product requires the presence of a standard 170 micron filter.

F. Personnel Qualifications

In the operating room, this procedure should be performed under the supervision of an attending anesthesiologist.

G. Reagents & Supplies

1. Standard CPDA-1 Blood Collection Bags. Expiration date will be checked prior to use.

2. Blood Collection Scale

3. Replacement fluid

4. A Central Line Monitor if necessary

5. Addressograph Specimen Labels

H. Quality Control

Yearly calibration of Blood Collection Scale by Anesthesia Technician.

I. Quality Assurance

1. A log book for ANH cases is kept in the anesthesia work room next to the CPD bags with patient's hospital labels and date of procedures.
2. Quarterly review of selected cases by the physician in charge of perioperative autologous blood transfusion.
 - a. Case mix
 - b. Blood transfusion requirements
 - c. Adverse events
 - d. Clinical outcomes

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