R ADAMS COWLEY
SHOCK TRAUMA CENTER
UNIVERSITY OF MARYLAND

Pennsylvania Society of Nurse Anesthetists

Current Trends and New Concepts in Peri-operative Fluid Management

Robert A. Sikorski, MD

Introduction

Perioperative targeted fluid therapy focuses on the patient who is preoperative, intraoperative or postoperative. Similar to septic ICU patients, this "goal directed" approach has shown promising results but continues to be inconclusive in determining the fluid type, timing and volume (rate and total). Contrary to our critically ill non-operative patients our patient group experiences the additional physiologic insult of the surgical procedure and the resultant volume shifts as well as blood loss.

Historical Fluid Therapy

The basis of goal directed (targeted) therapy is the "optimization" of cardiac preload, afterload, and contractility to balance oxygen delivery and oxygen demand. (Kehlit, 2009)Goals that are set by the clinician must be realistic for the patient and procedure. Optimizing physiologic parameters and volume strategies for short outpatient procedures may not be realistic. Aggressive volume replacement in patients with a complicated cardiac history may be equally impractical. These patients may be excluded from specific study groups but are part of our everyday practice. This leads us to the important questions of when to institute targeted fluid therapy and more importantly how to individualize this approach.

We are all familiar with the historical teaching of peioperative fluid replacement. These recommendations are based on general pathophysiologic fundamentals: (1) the preoperatively fasted patient is hypovolemic because of ongoing insensible perspiration and urinary output;(Holte K. e., 2002) (2) the insensible loss increases dramatically when the surgeon breaks the barrier of the skin; (Sear, 2005)(3) an unpredictable fluid shift toward the third space requires generous substitution;(Kaye & Kucera, 2005) (4) hypervolemia is harmless because the kidneys regulate the overload;(Watenpaugh & Yancy, 1992) (5) *"optimizing"* means "maximizing";(Noblett & Snowden, 2006)(6) blood volume cannot be assessed routinely.(Chappell, 2008)

There is an assumed hypovolemic state after hours of fasting. This commonly leads to preinduction or postinduction preoperative fluid loading of 2-cc/kg/ hour of fasting. In major abdominal surgery, this may have been followed by up to 10 cc/kg/hour in addition to 3 cc/kg/cc of blood loss. We now know that this is an "aggressive approach" to fluid therapy. This aggressive, and previously thought of as a standard, approach to volume replacement may lead to a 10 liter volume replacement after major abdominal surgery. A related perioperative body weight gain at approximately the same extent indicates that the contribution of insensible loss to intraoperative fluids is small.(Dawidson & Wilms, 1991) Crystalloids are not retained at the vascular barrier after having been infused intravenously; they are homogeneously distributed throughout the extracellular space. Four fifths are distributed into the interstitial space and only one-fifth remains intravascular.(Chappell, 2008) Isotonic colloids also do not stay totally within the intravascular space.(Jacob & Chapell, Clinical update: Perioperative fluid management, 2007) Also we must keep in mind that the indirect vasodilatory effect of anesthetics must be expected to terminate. The need for volume loading in the early perioperative period seems not necessary. Even after extended fasting, without concomitant bowel prep, intravascular blood volume seems to be within normal range.(Jacob & Chappell, 2008)We must then replace two types of fluid losses: (1) losses of insensible perspiration and urine (type 1); and (2) losses

occurring exclusively during trauma and surgery (type 2). The first type of loss affects the entire extracellular space and does not lead to a loss of colloid osmotic force from the intravascular space. The second loss is primarily an isolated intravascular deficit, including losses of all blood components.(Chappell, 2008) We should then treat each compartment's loss as a targeted component replacing what, and only what, is lost. In order to "individualize" targeted fluid therapy we need to be more precise in the way we monitor and assess the patient's deficit and replacement needs.

Individualizing Fluid Therapy

The traditional approach to the measurement of intravascular fluid volume has come under scrutiny during the past few decades. The "gold standard" methods such as central venous pressure monitoring and pulmonary artery catheter monitoring have seen a decline in routine clinical use.(Sandam, 2003) There exists a very poor relationship between central venous pressure (CVP) and blood volume, and recent data suggests that neither absolute CVP nor change in CVP over time reliably predict the hemodynamic response to a fluid challenge.(Richard, Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome:A randomized controlled trial, 2003) There still exist certain clinical scenarios such as acute air embolus (multi orifice catheter), acute pulmonary embolus and right heart infarction where central venous monitoring may have a role. Furthermore, a recent study showed that central venous catheter management utilizing an explicit management protocol led to fewer complications than pulmonary artery catheter (PAC) management in the treatment of acute lung injury, as well as an increase in ICU-free days. (Harvey, 2005)

Pulmonary artery catheterization has been the mainstay of hemodynamic monitoring throughout the past four decades, but is becoming increasingly controversial.(Chittock & Dhingra, 2004) An international consensus conference was held to develop recommendations for hemodynamic monitoring and implications for management of patients with shock.(Antonelli, Levy, & Andrews, 2007) Evidence based recommendations were developed after conferring with

experts and reviewing the pertinent literature, by a jury of eleven persons representing five critical care societies. The jury recommended against the routine use of the pulmonary artery catheter in shock and against the use of static preload measurements alone to predict fluid responsiveness. The use of the pulmonary artery catheter in critically ill patients with a high severity of illness and acute coronary syndrome (ACS) may provide a decrease in mortality rate but further randomized trials are needed. (Cohen, Kelly, & Menon, 2005)(Erickson & Martin, 2009) Over the past decade there has been a temporal improvement in survival at ARDSnet centers for ALI/ARDS not only because of the use of lower tidal volume ventilation and conservative fluid therapy but also with advancements in critical care, however the use of the PAC has not been implicated in this survival. (Yu, platt, Balck, & Sands, 2003) In one recent retrospective study, trauma patients managed with a PAC were more severely injured and had a high mortality.(Sandham, Hull, & Brant, 2003)(Richard, Warszawski, & Anguel, 2003) However, severely injured patients (Injury Severity Score, 25-75) who arrived in severe shock (base deficit of less than -11), and older patients (age 61-91 years of age) had an associated survival benefit when managed with the PAC. (Friese, Shafi, & Gentinello, 2006)

Addition of continuous mixed-venous oxygen monitoring to central venous pressure measurement has shown a benefit in Emergency Department and ICU management of patients in septic shock. (Gorcsan, Diana, & Lee, 1994) Decreased venous saturation is an indirect indicator of poor tissue perfusion and the need for resuscitation. Use of venous or tissue oximetry during emergency general surgery or acute trauma cases has not gained a large following. The dynamic response of these systems is felt to be too slow to guide therapy during active hemorrhage.

Other minimally invasive technologies, which have seen use recently for determination of fluid volume status, include echocardiography, trans-esophageal Doppler and arterial pressure-based cardiac output systems. The arterial pressure based cardiac output technologies also allow for assessment of volume responsiveness.

The use of echocardiography, both trans-thoracic and trans-esophageal, has gained popularity in the assessment of ventricular function (both systolic and diastolic) and volume status in the critically ill patient. Left ventricular function, assessment of global wall motion and ventricular filling by trans-thoracic echocardiography (TTE) can be utilized by the non-echocardiographer in the critical care setting. Basic parasternal, apical and sub-xyphoid views can be obtained in the majority of patients to assess real time hemodynamics. These skills can be acquired through specialized training under the guidance of an experienced echocardiographer or in a critical care training program with an emphasis on echocardiographic assessment. Trans-esophageal echocardiography (TEE) displays the left ventricle with superior definition to TTE. It is difficult, however, to view the apex in a non- foreshortened manner with TEE making TTE superior for apical views of the left ventricle. Basic left ventricular volume assessment and wall motion in TEE is done in the trans-gastric mid papillary short-axis view. This view is easy to obtain and subjectively can give the necessary information for basic hemodynamic assessment and guidance. Doppler echocardiography can also be used in the assessment of both right and left ventricular systolic function. The use of Doppler requires both experience and acceptable viewing angles for accuracy of measurement.Cardiac output measurements can be obtained using velocity time integrals in the right and left ventricular outflow tracts utilizing pulse wave and continuous wave Doppler. Mitral inflow measurements, with the pulse wave sample gate placed at the tips of the mitral leaflets, will allow assessment of diastolic function and diastolic hemodynamics. It must be remembered, however, that left ventricular loading conditions, heart rate, and left atrial and ventricular interactions influence Mitral inflow patterns. Pulmonary capillary wedge pressure can be estimated using color M-mode Doppler imaging and Doppler tissue imaging. (Bouhemad & Nicolas-Robin, 2003)(Choley & Payen, 2005) However, estimating PCWP by this method, in critically ill patients with circulatory shock and acute lung injury may not be accurate enough to adjust therapy. (Su, Huang, & Tsai, 2002) Because of the dependence on expensive technology and operator experience,

echocardiography— both trans-thoracic and trans-esophageal—remains an excellent diagnostic tool but a poor monitoring device.

Esophageal Doppler monitoring measures blood flow velocity in the descending aorta by way of an ultrasound transducer at the tip of a flexible probe. The probe must be placed so that the transducer faces the aorta and an aortic velocity signal is obtained. The estimation of stroke volume with this method relies on the measurement of stroke distance in the descending aorta (velocity time integral, VTI), which is then converted into systemic stroke volume via algorithms that vary slightly between manufacturers. (Seoudi, Paerkal, & Hanrahan, 2003) Esophageal Doppler has been shown to be a clinically useful alternative to thermodilution in determination of cardiac output, (Bein, Worthman, & Tonner, 2004) but suffers the common problem of noninvasive monitors in that the algorithms have been developed and much of the clinical validation studies performed in relatively healthy and normal patients. Algorithms used to derive familiar metrics such as cardiac output and stroke volume may be flawed in patients with the extreme physiology of severe shock or exsanguinating hemorrhage.

Most clinicians are now familiar with the concept of a goal directed approach for volume resuscitation and the treatment of early sepsis. (Rivers, Nyugen, & Havstad, 2001) There are many new technologies available to guide fluid resuscitation with a more dynamic approach rather than the use of the historical static parameters. Determining where the patient lies on their individual Starling curve, during the resuscitation process, may be more important than the fluid type being administered. (Hofer, Muller, & Furrer, 2005) Arterial pressure waveform systems function on the relationship between pulse pressure and stroke volume. Systolic pressure variation (SPV), the difference between maximum and minimum systolic pressure during one mechanical breath, has been shown to predict fluid responsiveness to volume loading. Concepts such as pulse pressure variation (PPV) and stroke volume variation (SVV) in ventilated patients have been extensively reviewed in the literature and found to be reliable predictors of volume responsiveness. Arterial based systems in clinical use today include the

PiCCO(Phillips), pulseCO (LiDCO, Ltd.) and the FloTrac/Vigileo (Edwards Lifescience). The systems are all minimally invasive. Some require calibration such as the LiDCO *plus* which utilizes Lithium dilution and a specialized lithium sensor, however, the LiDCO *rapid* does not require calibration and can be used with a standard arterial line. This system utilizes a validated PulseCO algorithm as well as pulse power analysis. The PiCCO system uses continuous pulse contour analysis but also requires a femoral arterial thermodiluton catheter. Any standard central venous line may be used for the transpulmonary thermodilution. Transpulmonary cardiac output and intrathoracic blood volume may be obtained with this system. Calculation of extra-vascular lung water using this device has been described elsewhere, but is not available in the United States.(Van der Heijden & Verheij, 2009) These features make this system relatively more invasive than the others. The FloTrac system (Edwards Lifescience) requires a special transducer, which is attached to the existing arterial line. The FloTrac transducer samples at a higher rate than the intra-operative monitoring systems currently in use (100Hz vs. 15-40 Hz). This system does not require calibration and calculates flow parameters every 20 seconds. The need for calibration is overcome by automatic vascular tone adjustments averaged over one minute.

All of the aforementioned systems calculate, through various methods, dynamic parameters such as stroke volume variation (SVV), pulse pressure variation (PPV), stroke volume (SV), stroke volume index (SVI), cardiac output (CO) and cardiac index (CI). SVV and PPV are more reliable indicators of volume responsiveness than CVP, PCWP, LVEDVI (left ventricular end diastolic volume index) and GEDVI (global end diastolic volume index). SVV and PPV have limitations in clinical use. They can be affected by alterations in ventilator settings, chest wall compliance and dysrhythmias, as well as by pharmacologically induced changes in ventricular and aortic compliance. (Hofer, Muller, & Furrer, 2005)

No one monitor or system has been shown to improve outcome by itself. Direct examination of cardiac filling and function is possible using echocardiography, but it cannot be used as a trending device. Use of minimally

invasive technologies for following trends has largely replaced traditional CVP and PA catheter based techniques in the general operating room, but the newer technologies suffer from a lack outcomes data. Accuracy and validation is needed in specific patient groups such as cardiac surgery patients and those in septic shock.(Fouche, Sikorski, & Dutton, 2010)

Perioperative Fluid

So we know that historical standards have been, but should not be, the norm and we have some idea of how to assess and individualize fluid therapy. I really don't want to say it but I must, "*crystalloid or colloid"?* There I said it! But, does it matter? The bulk of the literature on this issue is contradictory. Let's take a closer and more scientific approach.

As mentioned previously, a significant amount of crystalloid leaves the intravascular space for the interstitial space, the "classic" third space. In a review of perioperative fluid management Chappell *et al.,* eloquently proposes the question of the existence of the classic third space. Classic third space fluid losses have never been measured directly, and the actual location of the fluid losses remains unclear. (Brandstrup, 2006) Despite efforts to quantitate the third space using various tracer methods there has been a failure to identify this space.(Chappell, 2008) The opposite of a third space, a functional space, has been described. Within this space is contained the functional extracellular fluid (fECF). The fECF consists of the plasma, the interstitial space and the trans-cellular fluids. It is within the fECF that water and small solutes can easily exchange.

The layer of membrane bound proteoglycans and glycorpoteins, which lines the vascular endothelial surface, is the *endothelial glycocalyx.* This layer together with the endothelial cell layer is part of the double-barrier concept of vascular permeability opposing unlimited extravasation. (Rehm, Zahler, Lotsch, & Welch, 2004) Transcapillary fluid exchange seems then not to depend on the global difference between hydrostatic and oncotic pressures between blood and tissue. Rather, the hydrostatic and oncotic pressures between blood and the small space

directly underneath the endothelial glycocalyx but still inside the anatomical lumen of the vessel.(Jacob, Bruegger, & Rehm, 2007) Dimunition of the endothelial glycocalyx leads to platelet aggregation and leukocyte adhesion with a resultant increase in endothelial permeability and tissue edema. (Vink, Constantinescu, & Spaan, 2000)

Hypothermia must be mentioned in this discussion. It is known that mild hypothermia triples the risk of wound infection by reducing tissue oxygenation, but supplemental oxygen halves that risk. Fluid shifts are also dependent on core body temperature. With severe hypothermia, below 30^{o}C, there is a decrease in plasma volume, a decrease in central venous pressure and an increase in pulmonary and vascular resistance.(Hammersborg, Farstad, & Haugen, 2005) This should not be a frequent occurrence in non-cardiac surgery but may be a factor in trauma. Decreasing the surgically induced inflammatory mediators by using neuraxial anesthesia in addition to the other components may also protect the endothelium.(Holte & Kehlet, 2002)

The choice of volume replacement should then be considered as a drug with indications, contra-indications and side effects. Ischemic reperfusion, proteases, tumor necrosis factor α, oxidized low-density lipoprotein, and atrial natriuretic peptide has the power to degrade the glycocalyx. Surgical stress itself can cause the release of several inflammatory mediators that degrade the glycocalyx, however atrial natriuretic peptide is triggered by ***iatrogenic acute hypervolemia.*** (Yamaji, Ishibashi, & Takaku, 1985)(Kohl & Deutschman, 2006)

Our choices of volume replacement should now be targeted toward the specific types of loss and the timing of these losses. Timely replacement, and the extent of that replacement, can now be monitored minimally invasively and directed toward those specific compartments. Crystalloids should then be used to replace insensible perspirative losses and urine output to avoid infusing the entire extracellular space (type 1 shifting). Iso-oncotic colloids should be used to replace acute blood loss. To prevent crystalloid and protein shifting (type 2) it is essential to

protect the glycocalyx. The restoration of the circulating blood volume by infusing colloids to maintain intravascular normovolemia would reduce the interstitial load even if there were only a rudimentary competence of the vascular barrier.(Chappell, 2008).

Conclusion

The goal is to avoid collateral damage. As Chappell suggests, we change our thinking from fluid "therapy" to fluid "substitution". Plasma losses from the circulation should be replaced by iso-oncotic colloids. Timely replacement of acute visible blood loss should also be replaced by colloids. Naturally, in case of traumatic hemorrhage blood component therapy would be indicated. Insensible loss and urine output should be replaced with balanced crystalloid solutions but as previously mentioned these losses have always been over estimated. (Chappell, 2008) The volume of available literature is lacking substantial outcomes data and standardized protocols. Clinical practice differs between practitioners, institutions and regions. There are many ways to treat volume loss and replacement. I hope that in this syllabus I have exposed you to a more targeted approach to this controversial topic.

Goals can vary from heart rate and blood pressure to those of micro circulatory indicators of perfusion, oxygen delivery and utilization such as lactate and $ScV0_2$. Using a more scientific approach to understanding where the patient is on their starling curve with Doppler or stroke volume variation will avoid iatrogenic hypervolemia. Individualized, indicated fluid replacement, minimizing the surgically induced inflammatory mediators and shifting our thought process about volume replacement and assessment are the essential components of targeted perioperative fluid management.

Bibliography

Antonelli, M., Levy, M., & Andrews, P. (2007). Hemodynamic monitoring in shock and implications for management. *International Consensus Conference, april 27-28,2006. 33*, pp. 575-90. Paris: Int Care Med.

Bein, B., Worthman, F., & Tonner, P. (2004). Comparison of Esophageal Doppler, Pulse Contour Analysis and Real Time Pulmonary Artery thermodilution for the continuous measurement of cardiac output. *J Cardiothor Vasc Anesth , 18* (185-89).

Bouhemad, B., & Nicolas-Robin, A. (2003). Echocardiographic Doppler Assessment of PAWP in surgical patients with postoperative circulatory shock and acute lung injury. *Anesthesiology , 98* (5), 1091-1100.

Brandstrup, B. (2006). Fluid Therapy for the Surgical Patient. *Best Prac Res Clin Anesthesiol , 20*, 265-83.

Chappell, D. e. (2008). A Rational Approach to Perioperative Fluid Management. *Anesthesiology , 109*, 723-40.

Chittock, D., & Dhingra, V. (2004). Severity of illness and risk of death associated with Pulmonary Artery Catheter use. *Crit Care Med , 32* (4), 911-15.

Choley, B., & Payen, D. (2005). Non-invasive techniques for measurements of Cardiac Output. *Current Opin Crit Care Med , 11* (5), 424-29.

Cohen, M., Kelly, R., & Menon, V. (2005). Pulmonary Artery Catheterization in Acute Coronary Syndromes:Insights from GUSTO IIband GUSTO III Trials. *Am J Med , 118* (5), 482-88.

Dawidson, I., & Wilms, C. (1991). Ringers Lactate with and without 3% dextran-60 as volume expanders during abdominal aortic surgery. *crit Care Med* (19), 36-32.

Erickson, S., & Martin, G. (2009). Recent Trends in Acute Lung Injury Mortality:1996 - 2005. *crit Cre Med , 37* (5), 1574-79.

Fouche, Y., Sikorski, R., & Dutton, R. (2010). Current Management of the Critically Ill Surgical Patient:Changing Paradigms in Surgical Resuscitation. *Critical Care Medicine , 38* (9), S411-S420.

Friese, R., Shafi, L., & Gentinello, e. a. (2006). Pulmonary Artery catheter use is associated with reduced maortality in severely injured patients: A National Traum Data Bank analysis of 53,312 patients. *crit Care Med , 34*, 1597-1601.

Gorcsan, J., Diana, P., & Lee, J. (1994). Reversible Diastolic dysfunction after successful coronary artery bypass surgery. Assessment by Transesophageal Doppler Echocardiography. *Chest , 106*, 1364.

Hammersborg, S., Farstad, M., & Haugen, O. (2005). Time course variations in haemodynamics, plasma volume, and microvascular fluid exchange following

surface cooling:An experimental approach to accidental hypothermia. *Resuscitation , 65*, 211-9.

Harvey, S. (2005). Assessment of theclinical effectiveness of PA catheters in management of patients in intensive care(PAC-Man):A randomized trial. *lancet , 366* (9484), 472-77.

Hofer, C., Muller, S., & Furrer, L. (2005). Stroke Volume and Pulse Pressure Variation for Prediction of Fluid Responsiveness in Patients Undergoing Off-Pump Coronary Artery Bypass Grafting. *Chest , 128* (2), 848-54.

Holte, K. e. (2002). Compensatory fluid administration for preoperative dehydration: Does it improve outcome? *Acta Anaesthesiol Scand , 46*, 1089-93.

Holte, K., & Kehlet, H. (2002). Epidural anesthesia and analgesia:effects on surgical stress responses and implications for post operative nutrition. *Clin Nutr , 21*, 199-206.

Jacob, M., & Chapell, D. e. (2007). Clinical update: Perioperative fluid management. *Lancet* (369), 1984-6.

Jacob, M., & Chappell, D. (2008). Blood volume is normal after preopertive overnight fasting. *Acta Anaesthesiol Scand , 52*, 522-9.

Jacob, M., Bruegger, D., & Rehm, M. (2007). The Endothelial Glycocalyx affords compatability of Starling's Principle and high cardiac interstitial albumin levels. *Cardiovasc Res , 73*, 575-86.

Kaye, A., & Kucera, A. (2005). Fluid and electrolyte physiology. In Miller, *Anesthesia* (6th ed., pp. 1763-98). Philadelphia, PA, USA: Churchill Livingstaone.

Kehlit, H. e. (2009). Goal-directed Perioperative Fluid Management. *Anethesiology , 110*, 453-55.

Kohl, B., & Deutschman, C. (2006). The inflammatory response to surgery and trauma. *Curr Opin Crit Care , 12*, 325-32.

Noblett, S., & Snowden, C. (2006). Randomized clinical trial assessing the effect of Doppler-optimized fluid management on outcome after elective colorectal surgery. *Br J Surg* (93), 1069-76.

Rehm, M., Zahler, S., Lotsch, M., & Welch, U. (2004). Endothelial Glycocalyx as an additional barrier determining extravasation of 6% hydroxyethyl starch or 5% albumin solution in the coronary vascular bed. *Anesthesiology , 100*, 1211-23.

Richard, C. (2003). Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome:A randomized controlled trial. *JAMA , 290* (20), 2713-20.

Richard, C., Warszawski, J., & Anguel, N. (2003). Early use of the PA Catheter and outcomes in patients with shock and ARDS: a randomized controlled trial. *JAMA , 290* (20), 2713-20.

Rivers, E., Nyugen, B., & Havstad, S. (2001). Early Goal Directed Therapy in the treatment of Severe Sepsis and Septic Shock. Early Goal Directed Therapy Collaborative Group. *NEJM , 345* (19).

Sandam, J. e. (2003). A randomized controlled trial of the use of the pulmonary artery catheters in the high risk surgical patient. *N Engl J Med , 348* (1), 5-14.

Sandham, J., Hull, R., & Brant, R. (2003). A randomized controlled trial of the use of PA Catheters in high risk surgical patients. *NEJM , 348* (1), 5-14.

Sear, J. (2005). Kidney dysfunction in the postoperative period. *Br J Anaesth , 95*, 20-32.

Seoudi, H., Paerkal, M., & Hanrahan, A. (2003). The Esophageal Doppler monitor in mechanically ventilated patients; Does It Work? *J Trauma , 55*, 720-25.

Su, N., Huang, C., & Tsai, P. (2002). Cardiac Output measurement during Cardiac Surgery. Esophageal Doppler vs. PA Catheter. *Acta Anaestheiol Scan , 40*, 127-33.

Van der Heijden, M., & Verheij, J. (2009). Crystalloid or Colloid fluid loading and Pulmonary Permeability, Edema, and Injury in Septic and non-septic Critically Ill patients with Hypovolemia. *Crit Care Med , 37* (4), 1275-81.

Vink, H., Constantinescu, A., & Spaan, J. (2000). Oxidized lipoproteins degrade the endothelial surface layer :Implications for platelet-endothelialsurface layer. *Circulation , 101*, 1500-2.

Watenpaugh, D., & Yancy, C. e. (1992). Role of atrial natriuretic peptide in systemic response to acute isotonic volume expansion. *J Appl Physiol , 73*, 1218-26.

Yamaji, T., Ishibashi, M., & Takaku, F. (1985). Atrial natriuretic factor in human blood. *J Clinic Invest , 76*, 1705-9.

Yu, D., platt, R., Balck, E., & Sands, K. (2003). Relationship of PA catheter use to resource utilization in patients with severe sepsis. *Crit Care Med , 31* (12), 2734-41.