Characterizing Monitoring for the Diagnosis and Resuscitation of Shock Patients

by

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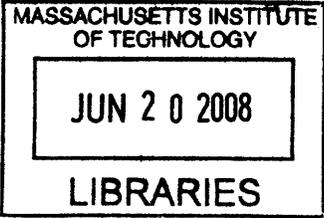
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Abstract

Many factors contribute to a company's decision to launch a product in a new market. The company must be able to identify a clinical need that the product will address and the market must be willing to pay for the new technology. This thesis explores the clinical and market need for an improved shock monitoring technology.

Shock occurs when there is not enough blood flow to adequately perfuse the body's organs. In the United States, about 500,000 patients go into sudden shock every year and half of these patients die. For millions of additional patients, shock is the final stage of a terminal disease. Despite advances in many other areas of medicine, shock continues to be a serious, life threatening condition. It is my hypothesis that the limitations of the current monitoring technologies contribute to the high mortality rate associated with shock.

In my research, I examined the currently available monitoring technologies and their use for the diagnosis and resuscitation of shock patients. I conducted an extensive review of the scientific literature to identify the limitations of the current monitoring technologies and to understand the challenges of diagnosing and treating shock. To supplement my research, I interviewed clinicians who treat shock patients and scientists who are trying to develop new shock monitoring technologies.

The clinicians confirmed that there is a critical need for improved shock monitoring technologies. However, for a new shock monitor to be successful, it will need to address the limitations of the current technologies. A well-designed clinical trial will be necessary to demonstrate that the new technology is sensitive and specific, clinically relevant, and easy to use.

Dedication

To my parents, Peg Franklin and Fred Jenkins, for always believing in me and encouraging me to pursue my goals.

To my brother, Jonathan, for his friendship and support.

To my fiancé, Josh Boyle, for his love, patience, and encouragement. I could not have made it through this program without him!

Forward

During my career, I hope to play a significant role in the commercialization of new medical device, pharmaceutical, or biologic products. I chose my thesis topic in the hope that it would help me develop the skills I need to accomplish this goal.

Last summer, I worked as an intern at Hemedex Inc., a small medical device company in Cambridge, Massachusetts. Hemedex has a tissue perfusion monitor that is currently marketed to neurosurgeons. As an intern, I focused my efforts on identifying additional therapeutic applications for the company's device. In conducting research on the possible applications, I became interested in shock monitoring. I hope that this thesis will provide companies like Hemedex with the insights necessary to improve shock management through the development and marketing of new monitoring technologies.

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Glossary of Terms

Afterload: The resistance against which the heart must eject its volume of blood. It is closely related to the aortic pressure.

Anasarca: An accumulation of fluid in the peripheral tissues that results in extreme generalized edema.

Cardiac Index (CI): A measure of cardiac performance that relates cardiac output (CO) to body surface area (BSA). CI = CO / BSA

Cardiac Output (CO): Volume of blood being pumped by the heart per minute. A normal adult heart pumps about 5 L of blood per minute. CO = SV * HR (SV – Stroke Volume and HR – Heart Rate)

Central Venous Pressure (CVP): A direct measure of blood pressure in the thoracic vena cava and an estimation of the right atrial pressure.

Crystalloid: Fluid, used during resuscitation, including lactated Ringer's solution, normal saline, Ringer's acetate, and balanced electrolyte solution.

Colloid: Fluid, used during resuscitation, including albumin, 5% plasma protein fraction, synthetic starches, and dextrans.

Hypoxia: A condition of inadequate oxygen in the blood, either generally or locally

Ischemia: A restriction in blood supply, generally due to factors related to the blood vessels

Lactate: Produced by exercising muscles from the conversion of glucose and metabolized by red blood cells metabolize. Lactate is released into the blood and

transported to the liver where it is converted back into glucose. In homeostasis, the production and destruction of lactate is balanced. However, when tissue is damaged, lactate production outpaces lactate clearance.

Mean Arterial Pressure (MAP): The average arterial pressure during a single cardiac cycle, which is considered to be the closest approximation of the perfusion pressure through the organs. MAP can be calculated from the systolic and diastolic blood pressures, but the relationship changes with changes to the heart rate. MAP = (CO * SVR) + CVP

Negative Predictive Value (NPV): A statistical measure of the proportion of patients with a negative test result who are correctly diagnosed as not having a particular condition. NPV = TN / (TN + FN), where TN is the True Negative (patients without the disease who receive a negative test result) and FN is the False Negative (patients with the disease who receive a negative test result).

Oliguria: Decreased production of urine

Positive Predictive Value (PPV): A statistical measure of the proportion of patients with a positive test result who are correctly diagnosed as having a particular condition. PPV = TP / (TP + FP), where TP is the True Positive (patients with the disease who receive a positive test result) and FP is the False Positive (patients without the disease who receive a positive test result).

Preload: Pressure stretching the ventricle of the heart after passive filling and atrial contraction, but before ventricular contraction.

Retroperitoneum: The anatomical space located behind the abdominal cavity.

Sensitivity: A statistical measure of how well a binary classification test correctly identifies that a patient has a particular condition. Sensitivity = TP / (TP + FN), where

TP is the True Positive (patients with the disease who receive a positive test result) and FN is the False Negative (patients with the disease who receive a negative test result).

Specificity: A statistical measure of how well a binary classification test correctly identifies that a patient does not have a particular condition. Specificity = TN / (FP + TN), where TN is the True Negative (patients without the disease who receive a negative test result) and FP is the False Positive (patients without the disease who receive a positive test result).

Systemic Vascular Resistance (SVR): The resistance of blood flow offered by the peripheral vasculature; affected by changes in blood vessel diameter and changes in blood viscosity. SVR = (MAP – CVP) / CO

Tissue Perfusion: The volume of blood that flows through a unit mass of tissue per unit time; presented in physiologic units of milliliters of blood per 100 grams of tissue per minute.

Chapter 1: Introduction

Importance of Blood Flow

Blood flow is necessary to sustain all living tissues in the body. The heart pumps approximately five liters of blood through ten miles of blood vessels about 1,000 times a day [13]. Blood flows from the heart, through the aorta, and into the arteries, the arterioles, and finally the capillaries. The capillary network is responsible for carrying blood to within 0.2 mm of every living cell in the body, delivering oxygen, nutrients, and

hormones to the tissues of the body and removing carbon dioxide, ammonia, and other waste. The figure to the right illustrates some of the important features of the vasculature, including the relative sizes and structures of the arteries, arterioles, capillaries, venules, and veins [17].
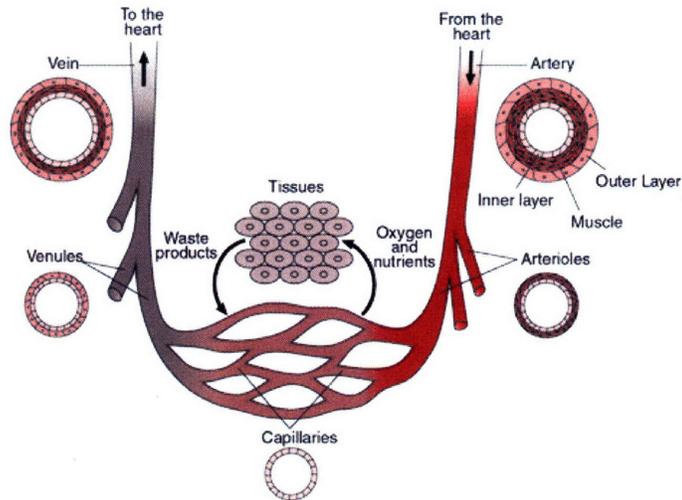
Blood flow can be described in terms of its systemic and regional properties. Systemic blood flow parameters, such as blood pressure and heart rate, provide a reasonable indication of a patient's general health, but they do not describe blood flow through the capillaries, so they are unable to predict oxygen delivery to the body's tissues. Tissue perfusion can be defined as "the rate at which the quantity of blood in a given mass or volume of tissue is replenished at the level of the capillary network" [35]. While tissue perfusion does not precisely describe oxygen delivery, by describing blood flow through the capillaries rather than through the arteries or veins, it more closely approximates oxygen delivery to the body's tissues. The amount of tissue perfusion depends on the patient's systemic vascular resistance, cardiac output, and effective volume of blood. Systemic vascular resistance is determined by the length and diameter of the blood

vessels and the viscosity of the blood. Cardiac output is determined by the heart rate and stroke volume. Effective blood volume refers to the quantity of blood and other fluids that are circulating through the arteries, veins, and capillaries. Inadequate tissue perfusion can be due to a decrease in systemic vascular resistance, a decrease in cardiac output, a decrease in blood volume, or a combination of the three parameters.

The effects of inadequate tissue perfusion are reversible if blood flow is restored quickly. However, inadequate perfusion over time can result in permanent cell injury because prolonged hypoxia causes cells to alter their metabolic processes. In hypoxic states, cell membranes stop functioning properly, leading to intracellular edema and/or the leakage of intracellular contents into extracellular spaces. These cellular changes eventually cause cell death and organ damage. Over time, hypoxia can result in multiple organ failure and death [4].

There is no gold standard for determining if the tissues of the body are being oxygenated. Rather, physicians use a combination of different methods to assess systemic blood flow and estimate tissue perfusion in high risk patients. Some of these methods include:

- **Physical evaluation of patient (mental status, skin color, temperature, sweating, capillary refill time):** The clinician's eye is one of his or her most valuable tools provided that it is integrated with a lifetime of experience. Hypoxic patients can progress from a normal mental state to anxious, agitated, lethargic, and eventually comatose [4]. As the peripheral vasculature constricts, the skin becomes pale and cool and the capillary refill time increases.
- **Blood pressure:** A decline in blood pressure, without any other known explanation, is an indication that the body's tissues might be deprived of oxygen. However, blood pressure is only useful if the clinician can determine the patient's baseline pressure because a low blood pressure could be normal for one patient and catastrophic for another. Clinicians will typically intervene if the patient's systolic blood pressure is less than 90mmHg.
- **Heart rate:** When the body's tissues are not being adequately oxygenated, the heart pumps faster.

- **Respiratory rate:** When the body's tissues are not being adequately oxygenated, the respiratory rate increases.
- **Urine output:** There is a minimum amount of urine that the body should excrete to ensure the removal of toxic byproducts. Since the kidneys are susceptible to decreases in blood flow, a decline in urine output can indicate that the body's tissues are becoming ischemic.
- **Blood gases (i.e. pH, lactate):** The normal pH of the blood is about 7.8, but when the body's tissues are hypoxic, they are forced to undergo anaerobic metabolism, which decreases the pH. Anaerobic metabolism also creates lactate as a byproduct.

The physical evaluation and blood pressure provide crude, but very useful information about a patient. While not sufficient at detecting small changes in tissue oxygenation, they provide a preliminary indication of a patient's status. Trends in these parameters can also be very helpful in determining if a patient is getting better or worse or how a patient is responding to therapy. Increases in heart rate and respiratory rate are two of the body's first efforts to compensate for inadequate oxygenation. Urine output gives the clinician a picture of what is happening in the kidney, one of the body's vital organs. If the kidney becomes ischemic, the body stops producing urine, which alerts the clinician to intervene. Blood gases provide the closest approximation to what is happening at the tissue level, but they are a late warning sign of tissue hypoxia.

While each of these parameters provide information that enables a clinician to better treat the patient, they do not identify the underlying condition that is causing the hypoxia, so they do not provide a means of preventing patients from going into shock. They are also not adequate at determining when a patient has been sufficiently resuscitated, so clinicians typically rely on a combination of the available parameters.

What is Shock?

Clinical Problem

Clinicians have been describing shock for hundreds of years. For example, in 1872, Dr. SG Gross defined shock as a "manifestation of the crude unhinging of the machinery of life" [24]. Today's definitions of shock are less poetic and more descriptive of the underlying mechanisms. Dorland's Medical Dictionary defines shock as "a condition of profound hemodynamic and metabolic disturbance characterized by failure of the circulatory system to maintain adequate perfusion of vital organs" [3]. The Advanced Trauma Life Support Manual defines shock as "an abnormality of the circulatory system that results in inadequate organ perfusion and tissue oxygenation" [24].

There are many underlying medical conditions that can cause a patient to go into shock. As a result, shock has been divided into subtypes based on the general cause of the inadequate tissue perfusion.

- Hypovolemic Shock: Hypovolemic shock is caused by an inadequate volume of blood due to hemorrhage or a loss of fluid. This is the most common cause of shock and it often develops after a trauma or surgery.
    - "Shock is a complication of many traumatic conditions and is the cause of up to half of all deaths from trauma: 40 percent due to acute hemorrhage and up to 10 percent due to multiple organ failure long after the initial cause of shock has been controlled" [4].
- Cardiogenic Shock: Cardiogenic shock is caused by a cardiac defect that prevents the heart from pumping sufficiently. Cardiogenic shock can also be described as obstructive shock when it is caused by mechanical factors that interfere with the filling or emptying of the heart or large vessels. The mechanisms of cardiogenic shock include impaired myocardial contractility, abnormalities of cardiac rhythm, and cardiac structural disorders. Cardiomyopathies, arrhythmias, mechanical defects, and obstruction can all result in cardiogenic shock, but the most common cause is heart attack.

- o There are about 280,000 cases of cardiogenic shock per year in the United States [13].
- o Less than 10% of patients with a heart attack will develop cardiogenic shock, but the mortality rate for these patients is about 50% [19].
- Distributive Shock: Distributive shock is caused by a decrease in systemic vascular resistance (vasodilation) most often due to sepsis, anaphylaxis, or another condition that activates the systemic inflammatory response. Rarely, distributive shock can be caused by a severe injury to the brain or spinal cord. This form of shock is called neurogenic shock and it results from the sudden loss of autonomic and motor reflexes below the injury level, causing the vessel walls to relax. Distributive shock can also be the result of hypovolemic or cardiogenic shock that has persisted for several days.
    - o "Sepsis affects 500,000 people in the US every year; about half of them develop septic shock, and 125,000 die from it" [13].
    - o Sepsis is the leading cause of death in the noncoronary intensive care unit, accounting for over $17 billion in healthcare costs [32].

Classification of Shock [25]

Parameters	Type of Shock			
	Hypovolemic	Cardiogenic	Obstructive	Distributive
Preload, filling pressures, end-diastolic volumes	↓	↑	↑↓	↓
Pump, cardiac output	↓	↓	↓	↑
Afterload, systemic vascular resistance	↑	↑	↑	↓
Systemic oxygen delivery	↓	↓	↓	↑
Systemic oxygen consumption	↑	↓	↑↓	↑↓
Systemic oxygen extraction ratio	↑	↑	↑	↓
Global oxygen balance, SvO2 or ScvO2*	↓	↓	↓	↑
* SvO2, mixed venous oxygen saturation; ScvO2, central venous oxygen saturation.				

In the United States, 500,000 people go into sudden shock every year and about half of these patients die [13]. For millions of additional patients, shock is the final stage of a terminal disease. While physicians have understood the causes of shock for many years,

prevention and treatment continue to be extremely difficult. In fact, many of the diagnostic techniques and therapeutic interventions have not changed significantly in the last 20 years.

Regardless of the underlying cause, many of the clinical symptoms of shock are similar. These can include hypotension, cold or clammy skin, oliguria, a decline in mental status, and metabolic acidosis. These symptoms develop as the patient progresses from pre-shock to shock and finally to end-organ dysfunction and death [6]. In pre-shock, the body is able to compensate for the reduction in perfusion. The extent and duration of compensation varies significantly depending on the age and health of the patient. Clinical symptoms may be entirely absent during this phase. When a patient enters the shock phase, the body is no longer able to compensate for the inadequate perfusion. During the end-organ dysfunction phase, irreversible organ damage occurs.

Shock is a life threatening condition and must be managed with immediate intervention. Dr. R. Adams Cowley, founder of the R Adams Cowley Shock Trauma Center and Maryland EMS System in Baltimore, Maryland, is credited with developing the concept of the "Golden Hour" of shock management. He explained:

> "There is a golden hour between life and death. If you are critically injured you have less than 60 minutes to survive. You might not die right then; it may be three days or two weeks later – but something has happened in your body that is irreparable" [37].

While the early phases of shock are reversible, late shock is not reversible. Therefore, early care that is provided in the emergency room plays a critical role in determining a patient's outcome. In the case of hypovolemic and septic shock, fluids are administered intravenously to restore tissue perfusion. However, there is a threshold for reperfusion. If too much fluid is administered, the patient can sustain additional organ damage from over-resuscitation. For example, if the vasculature has been vasoconstricted for a period of time, a sudden restoration of blood flow will provides a means of distributing the metabolic toxins that accumulated in the hypoxic tissue [4]. Acute renal failure and

pulmonary edema are two injuries that can result from the distribution of metabolic toxins and inflammatory mediators [8]. The timing and aggressiveness of fluid resuscitation should also be considered in patients that are actively bleeding because it can increase bleeding, by diluting the clotting factors and increasing the blood pressure [11].

Market Opportunity

In 2004, Dorland Healthcare Information projected that the US patient monitoring market would reach $4.3 billion in 2008 [34]. While the total market is growing, much of that growth is driven by self-monitoring devices used in the home and the emergence of alternate sites of care, including outpatient surgical centers.

The US hospital-based vitals signs monitoring market generated $804.4 million in 2004 [9]. Vital signs monitors measure a variety of different parameters, including the patient's temperature, respiratory rate, pulse rate, capnography, blood pressure, and blood oxygenation. Critical care units are responsible for over 50% of the revenue that is generated from patient monitor sales [9]. ICU patients only occupy about 10% of inpatient beds, but they account for almost 30% of acute care hospital costs, or $180 billion per year in the United States [32]. The patient monitoring market is fairly saturated, so current development efforts are primarily focused on replacing the current, invasive technologies with non-invasive technologies that measure similar parameters. Philips Medical Systems and GE Healthcare are the leading players, representing over 70% of the hospital vital signs patient monitoring market [9].

Hemodynamic monitoring represents a growing segment of the patient monitoring market. In the US, the market forecast for hemodynamic monitoring, which includes pulmonary artery catheters as well as non-invasive and minimally invasive technologies, is projected to reach revenues of $154 million by 2012 [32]. The non-invasive and minimally invasive segment is projected to grow at a compound annual growth rate of 20% over the next 5 years, while pulmonary artery catheter sales are projected to

decrease from $98.1 million in 2007 to $85.7 million in 2012 [32]. The use of pulmonary artery catheters has been decreasing for several years. In fact, between 1993 and 2004, PAC use declined 65% [33]. At the annual meeting of the Society of Critical Care Medicine in February 2008, clinicians stressed the need for improved hemodynamic monitoring technologies for the diagnosis of sepsis and shock [32].

US Market Forecast for Noninvasive and Minimally Invasive Cardiac Output Monitoring Systems [32]

Year	Sales	Annual Change
2006	$22.5 million	
2007	$31.5 million	40.0%
2008E	$38.0 million	20.6%
2009E	$45.0 million	18.4%
2010E	$52.0 million	15.6%
2011E	$60.0 million	15.4%
2012E	$69.0 million	15.0%
CAGR (2006 – 2012E)	20.5%	

Objective of Thesis

Despite advances in many other areas of medicine, shock continues to be a serious, life threatening condition. This raises a number of issues and questions. For example, what drives the high mortality rates of shock patients? Are the diagnostics or therapeutics insufficient? Is the process or approach to treating patients insufficient? Does the natural history of the condition cause patients to deteriorate before a clinician is able to intervene? It is my hypothesis that the limitations of current monitoring technologies contribute to the high mortality rate associated with shock.

My goal is to characterize the current monitoring and management techniques and to analyze the need for an improved monitoring technology. Prior to conducting my

analysis, I identified two relevant patient groups, those at risk of going into shock and those that are being resuscitated from shock.

In order to better ascertain if the current monitoring technologies are sufficient, I define the standard of care for monitoring patients that are at risk of going into shock, and for monitoring patients that are being resuscitated from shock. I expect that there is not one universal standard of care, but rather, heterogeneity in the protocols used at various hospitals and by different clinicians.

To assess my hypothesis, I empirically ask the following questions.
- How do clinicians manage patients that are at risk of going into shock?
- How do clinicians manage patients that are in shock?
- What monitoring technologies are used and in what combination?
- Under what conditions do clinicians intervene?
- What goes wrong? Why? How often?
- What do clinicians do when something goes wrong and what is the outcome?
- Would an earlier warning of a patient's entry into shock change the management or outcome?
    - How much earlier would be necessary?
    - How would the management or outcome change?
- Would an improved measurement of tissue perfusion change the management or outcome of patients that are in shock?
    - What kind of improvement is necessary?
    - How would the management or outcome change?

Chapter 2: Methodology

Review of Scientific Literature

To identify the limitations of the current monitoring technologies and assess the need for an improved tissue perfusion monitoring device, I conducted an extensive review of the leading scientific journals. I identified the challenges of preventing and managing shock as well as the currently available monitoring technologies, their uses and their limitations. I also conducted research on technologies that have been developed, but not widely adopted, to help identify the challenges that a new technology would undoubtedly face.

Interviews

While my research was useful in identifying monitoring technologies and describing some of their limitations, I needed to understand which devices are actually used and in what combinations. I also needed to understand how clinicians perceive the limitations of the available monitoring technologies. I therefore interviewed clinicians to determine how they use the available monitoring technologies to manage patients that are either at risk of going into shock or are being resuscitated from shock. In addition to clinicians, I interviewed scientists who are working to improve the management of shock patients by developing new monitoring technologies or by improving the use of the current monitoring technologies.

Developing the Interview Guide

I created a detailed interview guide to focus my interviews on the key issues. A brainstorming session with my thesis advisors, a BEP Advisory Board member, and a former BEP student served as a starting point for the interview guide. In addition to focusing the interview questions on the most relevant topics, I also designed the guide to support a one hour interview. I circulated a draft interview guide to the group for feedback prior to finalizing the questions and structure.

I designed the questionnaire to include a majority of open ended questions. While it can be challenging to aggregate the responses to open-ended questions, this format was the most appropriate for my needs because it did not constrain the responses of my interviewees. It also allowed the clinicians to raise issues that I had not previously considered. I avoided leading questions and I allowed my interviewees to speak freely, rather than stopping them after their initial responses. At the conclusion of each interview, I asked the clinicians to rate their overall satisfaction with the current monitoring technologies and the value of a tissue perfusion monitor.

I scheduled my first interview with a clinician who was interested in shock and familiar with my thesis project. This enabled me to pilot test the questions and the overall structure of the interview guide. After the first interview, I made several minor changes to the structure of the guide. The final interview guide can be found in Appendix A.

Selection of Interviewees

I set a goal of interviewing 10-15 clinicians from at least five institutions. This relatively small number of interviews would not be sufficient for a robust statistical analysis, but it provides the diversity that I need to supplement my research, further characterizing shock monitoring. I acknowledge that a more extensive study might be necessary to justify a significant investment in the development of a new monitoring technology.

I leveraged my network to schedule interviews with clinicians at several hospitals. Additionally, since shock patients are treated in the emergency room, the intensive care unit, and the operating room, I selected clinicians that monitor patients and provide care in each of these environments. By interviewing a diverse group of clinicians, I minimized the risk of hospital-specific or environment-specific perspectives. However, I deliberately selected a majority of anesthesiologists. One of the primary roles of an anesthesiologist is to monitor the vital signs of patients to make sure that their health status is stable or improving. Since anesthesiologists spend a significant amount of time monitoring patients for the signs of shock, they were ideal interview candidates. I

requested interviews with twelve clinicians at seven hospitals and three scientists and was successful in scheduling interviews with the following twelve individuals.

Michael Bailin, M.D.	Anesthesia and Critical Care at Massachusetts General Hospital, Boston, MA
Howard Corwin, M.D.	Critical Care Medicine at Dartmouth-Hitchcock Medical Center, Lebanon, NH
Mark Dershwitz, M.D., Ph.D.	Vice Chair of Anesthesiology at University of Massachusetts Medical Center, Worcester, MA
Richard Dutton, M.D., M.B.A.	Chief of Trauma Anesthesiology at University of Maryland Medical Center, Baltimore, MD
Stuart Forman, M.D.	Anesthesia and Critical Care at Massachusetts General Hospital, Boston, MA
George Frendl, M.D., Ph.D.	Anesthesiology, Perioperative, and Pain Medicine at Brigham and Women's Hospital, Boston, MA
Edward Kelly, M.D.	General and Gastrointestinal Surgery at Brigham and Women's Hospital, Boston, MA
James Pomposelli, M.D., Ph.D.	Hepatobiliary Surgery & Liver Transplantation and General Surgery at Lahey Clinic, Burlington, MA
Jose Salinas, Ph.D.	Director of the Trauma Systems Development, US Army Institute of Surgical Research, Fort Sam Houston, TX
Babs Soller, Ph.D.	President of Reflectance Medical and Professor of Anesthesiology at University of Massachusetts Medical School, Worcester, MA
George Velmahos, M.D., Ph.D.	Chief of Truama, Emergency Surgery, and Surgical Critical Care at Massachusetts General Hospital, Boston, MA
Charles Wade, Ph.D.	Senior Scientist, US Army Institute of Surgical Research, Fort Sam Houston, TX

To provide some additional context for my interviews, I spent time in an intensive care unit, several operating rooms, and a trauma center. I accompanied Dr. Luca Bigatello, Director of Critical Care, as he conducted rounds in the intensive care unit at Massachusetts General Hospital. I joined Dr. Michael Bailin as he oversaw the anesthesiology team in several operating rooms at Massachusetts General Hospital. Dr. Richard Dutton and his anesthesiology staff gave me a tour of the Shock Trauma Center at the University of Maryland Medical Center.

Chapter 3: Monitoring Technologies

Shock Monitoring Technologies

Patient monitoring is extremely important in the intensive care unit, the operating room, and the emergency department. Vital signs, including body temperature, blood pressure, respiratory rate, and pulse rate, are continuously monitored for all critically ill patients. Changes in any of these parameters can indicate a decline in the patient's health status and the need for intervention. However, while these parameters provide a general indication of the patient's status, they are not always sufficient to determine if a patient is at risk for going into shock. Physicians rely on data from a combination of different monitoring technologies to determine if a patient is going into shock, and to manage the treatment of shock patients.

Arterial Catheter

An arterial line provides a means of continuously measuring blood pressure and it provides access to the blood, allowing the clinicians to evaluate the complete blood count, electrolytes, glucose, blood gases, and coagulation parameters. Lactate is a particularly important parameter in shock patients because it gives an indication of the severity and duration of shock. Lactate can also be used to guide resuscitation because lactate clearance indicates that the patient is responding to the therapeutic intervention [20].

In 2005, Edwards launched the FloTrac system, which uses an arterial catheter and continuous self-calibration to provide cardiac output, stroke volume, stroke volume variation, and systemic vascular resistance. The system achieved sales of almost $30 million in 2007 [32].

In the United States, about 8 million arterial lines are placed every year [29]. Arterial catheters are commonly used because they provide valuable hemodynamic information and serious complications from placement are extremely rare. However, arterial lines

take time to insert. This can limit the use of arterial lines, especially during the early monitoring of shock patients that occurs in the emergency room.

Central Venous Catheter

Central venous catheterization provides a means of continuously measuring superior vena caval oxygen saturation, which is a surrogate marker of mixed venous oxygen saturation. Mixed venous oxygen saturation is probably the most specific marker for tissue perfusion, but it requires the use of a pulmonary artery catheter. There is some evidence that controlling resuscitation to achieve target superior vena caval oxygen saturation values can improve survival [22, 25]. However, the relationship between superior vena caval oxygen saturation and mixed venous oxygen saturation varies significantly between healthy volunteers and critically ill patients. This makes it difficult to determine an appropriate target for superior vena caval oxygen saturation and prevents clinicians from being able to confidently estimate mixed venous oxygen saturation in critically ill patients.
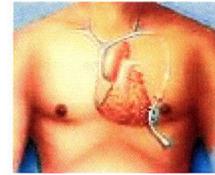
Echocardiography

Echocardiographic techniques use standard ultrasound to provide two-dimensional images of the heart. These images provide clinicians with information about the size, shape, and pumping function of the heart. Transesophageal echocardiography is often used during cardiac surgery because it provides many different views of the heart. A specialized probe, with an ultrasound transducer, is placed in the patient's esophagus. Since the heart is located within millimeters of the esophagus, transesophageal echocardiography provides much clearer images than a traditional echocardiogram. Viewing the heart enables the clinician to determine if there are any structural abnormalities that could impair blood flow. The addition of a Doppler transducer to the echocardiographic device enables the measurement of the blood velocity.
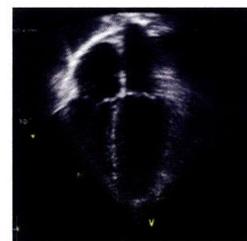
Esophageal Doppler Monitor (EDM)

The esophageal Doppler monitor provides a minimally invasive and low cost method of continuously monitoring hemodynamic variables. The parameters that can be derived from EDM include peak velocity in the descending aorta, flow time, and heart rate. These variables can be used to calculate cardiac output, stroke volume, and cardiac index. The EDM is inserted similarly to a nasogastric tube and has been used to guide fluid management in the OR and ICU [20]. In May 2007, CMS confirmed that it would provide coverage on a national basis for the use of esophageal Doppler monitoring of blood circulation [32].

Foley Catheter

A Foley catheter is a thin, sterile tube that is inserted into the bladder to drain urine. While the Foley catheter does not measure or estimate blood flow, the device is important because it enables clinicians to measure the amount of urine being produced by the kidneys. Since a decline in urine output is associated with inadequate perfusion of the kidneys, the Foley catheter provides a surrogate marker for renal perfusion. Moreover, since the kidneys are considered to be vital organs, their perfusion status can help clinicians to understand the status of other abdominal organs.
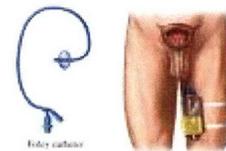
Gastric Tonometry

Gastric tonometry is a method of indirectly measuring the pH of the gastric intramucosal cells to determine if and when these cells become hypoxic. The gastric tonometer is inserted into the stomach through the nasogastric or orogastric route. After insertion, a small amount of saline is pumped into the balloon and left to equilibrate. A sample of arterial blood is taken and the blood and aspirated
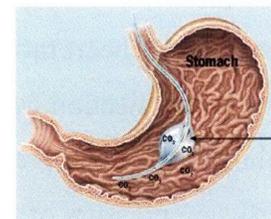
saline are analyzed in a blood gas analyzer. The intestinal pH is calculated from the saline PCO_2 and the arterial bicarbonate concentration.

This measurement is relevant because a low gastric mucosal pH could provide an early warning that a patient is going into shock. Gastric intramucosal pH could also be used to determine if a patient has been sufficiently resuscitated. There is a general consensus that a low gastric intramucosal pH is associated with a poor outcome. However, while treatment with fluids raises the pH, the clinical significance of this increase is questionable because there is no evidence that it improves patient outcomes [7]. Additionally, the device can take up to 30 minutes to insert and calibrate, which poses a significant logistical burden. Based on these findings, many scientists question whether intramucosal pH is a good measure of intestinal mucosal oxygenation and the gastric tonometer has not been widely adopted. It has recently been shown that sublingual mucosal carbon dioxide correlates well with gastric mucosal carbon dioxide and illness severity in septic patients [20]. Since these devices are much easier to use than gastric tonometers, they may become more commonly utilized to monitor shock patients.

Pulmonary Artery Catheter (PAC)

When the pulmonary artery catheter, also called the Swan-Ganz catheter, was first developed in the late 1960s, it provided data that was not otherwise available. As a result, it experienced rapid, widespread adoption. However, by the late-1980's, physicians and scientists became concerned about the PAC's invasiveness and its still unknown therapeutic utility.

Today, the pulmonary artery catheter provides a means of continuously measuring temperature, heart rate, mixed venous saturation of oxygen, cardiac output, right ventricular ejection fraction and end-diastolic volume, central venous pressure, and pulmonary arterial pressure [22]. Mean arterial pressure, which is believed to reflect the perfusion pressure of the vital organs, can be calculated from the measured indices. Mixed venous saturation is probably the most specific marker for tissue perfusion, but

calibration can be difficult for the patients that need it the most. As a result, it has never been validated in trauma patients. However, it can be used in septic shock patients because for these patients, resuscitation efforts do not interfere with efforts to control the source of the sepsis.

Despite the vast amount of data that is available from a pulmonary artery catheter, there is little evidence that the information leads to improvements in patient outcome. In fact, there have been five large randomized trials of PAC use and none of them has demonstrated a significant clinical benefit to patients [27]. Additionally, there are risks associated with the insertion of a PAC. These risks include arterial puncture, infection, arrhythmias, and pneumothorax. While several studies have concluded that the risks outweigh the benefits, a randomized controlled trial by Richards et al. found that "clinical management involving early use of a PAC was not associated with significant changes in mortality and morbidity among patients with shock" [25]. The use of pulmonary artery catheters continues to be a controversial issue among the academic and medical communities and in recent years, the utilization of PACs has declined significantly.
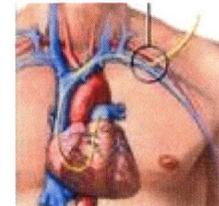
Pulse Oximetry

The pulse oximeter is a medical device that indirectly measures the amount of oxygen in a patient's blood and changes in blood volume in the skin. The device is able to detect blood flow through the arteries and arterioles in the subcutaneous tissue by illuminating the skin with the light from a light emitting diode (LED) and measuring the amount of light that is either transmitted or reflected to a photodiode.

Pulse oximeters are often placed on the finger or ear, but in cases of shock, when blood flow in the periphery can be reduced, the pulse oximeter can be placed on the head. Typical uses for pulse oximeters include the monitoring of heart rate, respiration, depth of anesthesia, and hypo- / hyper-volemia. The detection of a pulse is critical for the pulse

oximeter to function. While pulse oximeters are beneficial, they do not provide a complete measure of circulatory sufficiency. For example, if there is insufficient blood flow or insufficient hemoglobin in the blood, the tissue can suffer hypoxia despite high oxygen saturation.

Limitations of Current Technologies

Questionable Impact on Outcomes

One of the most serious limitations in the currently available technologies is a lack of useful data to quantify the therapeutic benefits and impact on outcomes. While studies have been and continue to be published, there is significant controversy surrounding their conclusions. For several of the available technologies, there are strong opponents and proponents who site conflicting studies to defend their position [7, 26, 28, 24]. Gastric tonometry and pulmonary artery catheters are two of the most controversial technologies for shock monitoring and as a result, they are in limited use today.

Systemic, Not Regional Blood Flow

Another limitation of the currently available technologies is that they measure systemic, rather than regional, blood flow. Since the body is able to compensate for a certain level of cardiac insufficiency, systemic measures may not provide the earliest signal that a patient is at risk of going into shock. Additionally, during resuscitation, the systemic measures may return to normal before the tissues have been sufficiently perfused. Therefore, it is likely that an accurate measure of regional blood flow would provide a faster and more sensitive indication of a patient's entry into shock or of a patient's adequate resuscitation from shock. However, there are limitations to monitors that measure regional blood flow. While the heart, brain, and abdominal organs are understood to be the body's vital organs, it is not clear which of these organs, if any, would be the most appropriate for measuring regional blood flow.

Technologies in Development

Over the past 10 or 15 years, several new hemodynamic monitoring technologies have become available and a few of them, including gastric tonometry and PACs inserted into the hepatic vein, have focused on regional blood flow. However, despite the perceived improvements of measuring regional rather than systemic blood flow, the technologies have failed to gain widespread market acceptance [22]. The most common reason why these technologies failed is because they were not associated with improved outcomes. Monitoring for the sake of monitoring is not useful. Any new monitoring technology must be associated with an improved outcome, either by altering the natural progression of the disease or by altering the treatment. Today, the quest for an improved monitoring technology continues.

Thermal Diffusion

Hemedex has developed a tissue perfusion monitor that uses a proprietary thermal diffusion technology to provide a continuous and accurate measure of absolute regional blood flow, in milliliters per minute per 100 grams of tissue, at the capillary level. The device consists of a patient monitor, a cable, and a probe. The probe, which is 1 mm in diameter, is inserted into the tissue of interest for up to 10 days. The device measures the energy needed to maintain a temperature differential between two temperature sensors and a complex computer algorithm uses this energy measurement to calculate the blood flow in the volume surrounding the probe.

The Hemedex tissue perfusion monitor has FDA approval for "extravascular monitoring of microcirculation blood flow in buried tissues" and is currently being marketed to neurosurgeons. The probe costs about $1,000 and is being used to monitor brain perfusion during cerebral aneurysm surgery, during recovery from subarachnoid hemorrhage when the patient is at risk of vasospasm, and following traumatic brain injury. While research on shock patients is not yet available, data from animal

experiments indicate that this technology could provide an earlier warning of a patient's entry into shock and improved monitoring during resuscitation from shock.

Near Infrared Spectroscopy

Near infrared spectroscopy is a non-invasive monitoring technology that continuously assesses tissue oxygen saturation, using wavelengths of near infrared light to illuminate the tissue below a sensor placed on the skin. Tissue oxygen saturation measurements differ from pulse oximetry measurements in that pulse oximetry measures the systemic oxygen saturation of the arterial blood [36].

Hutchinson Technologies has a commercially available spectroscopy system that uses near infrared spectroscopy to determine the average tissue oxygen saturation across skin, fat, and muscle, using proprietary algorithms. It permits the continuous, noninvasive measurement of tissue hemoglobin oxygen saturation and has been shown, in clinical trials, to be more reliable than base deficit and SvO_2 as an index of hemorrhagic shock [2].

Reflectance Medical is developing a non-invasive technology to monitor tissue pH, tissue oxygen saturation, and hematocrit for the early detection of hemorrhagic and septic shock. The company uses a continuous-wave spectroscopic instrument to determine muscle oxygen saturation. In a recent trial, Reflectance Medical demonstrated that its device was able to detect patients in mild and moderate shock while the Hutchinson Technologies' device was only able to detect severe shock [30]. Much of the company's development has been in collaboration with the United States Army. The U.S. Army is interested in identifying patients before they go into shock because once they go into shock, it is often too late.

Chapter 4: Managing Patients in Shock

In managing patients in shock, the clinician's primary goal is the restoration of tissue perfusion and oxygenation. However, the means of restoring tissue perfusion differ depending on the underlying mechanism of shock. Hypovolemic and distributive shock are typically managed with fluid resuscitation while cardiogenic shock is often managed by administering agents that increase the pumping function of the heart.

Advanced Trauma Life Support

Trauma and post-operative bleeding are two of the leading causes of hypovolemic shock. In fact, about 40% of the deaths from injury are due to shock from blood loss [4]. The American College of Surgeons has developed a curriculum, Advanced Trauma Life Support (ATLS), which has become the standard for diagnosing and managing trauma patients around the world [4]. The ATLS guides the clinician to provide the ABCs (airway support, mechanical ventilation, and circulatory support), if necessary, and then check for any neurologic disability or other injuries. A bolus of fluid is administered to determine if the patient is a "responder," a "transient responder," or a "nonresponder." As a general rule, responders are not actively bleeding while transient responders and nonresponders are actively bleeding. In the case of transient responders or nonresponders, the clinician must quickly identify the source of the blood loss and look for other causes of shock, including a high spinal cord injury, tension pneumothorax, and cardiac tamponade. For all massive trauma patients, the ATLS curriculum provides guidance on looking for blood loss. Computed tomography imaging is one of the most useful tools for identifying the source of the blood loss. The ATLS also guides the clinician through the resuscitation process.

Resuscitation Protocols

The following diagram provides an algorithm for the resuscitation of a patient in shock [16]. In patients with tachycardia and/or hypotension, clinicians begin with the ABC's,

securing the airway, assuring that the patient is breathing, and providing any necessary circulatory support. If the vital signs are still unstable, the clinician is directed to insert a central line and begin monitoring the patient's central venous pressure. If the central venous pressure is low, the clinician should administer fluids, either crystalloid or blood depending on the patient's hematocrit, until the central venous pressure rises. If the vital signs no not improve, the clinician should consider inserting a pulmonary artery catheter to measure the cardiac index and pulmonary capillary wedge pressure. Depending on the values of these parameters, the clinician should administer additional fluids or an inotropic agent, which increases the contractility of the heart.
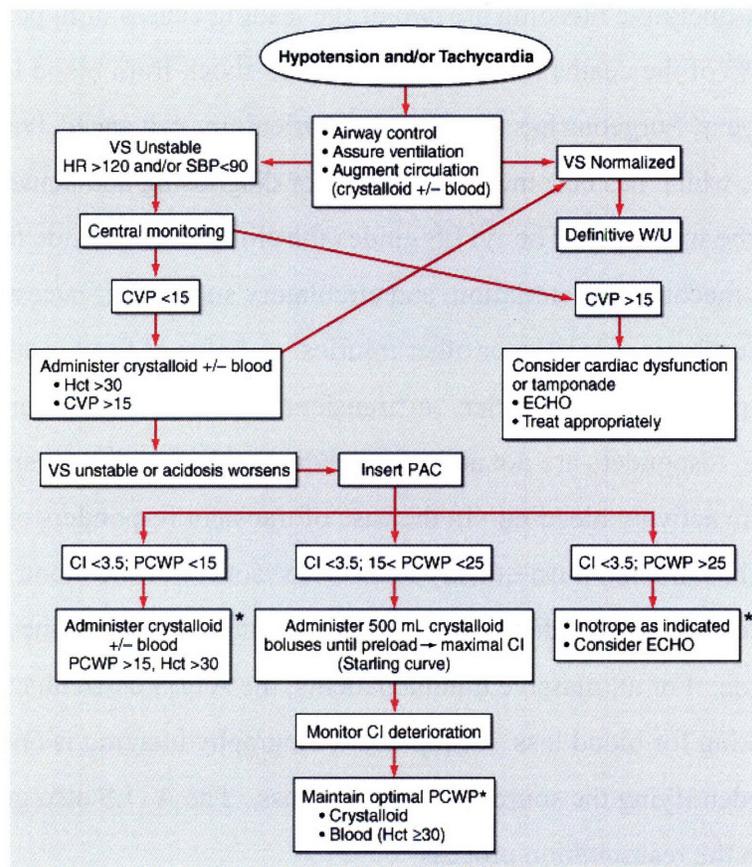
VS (vital signs), HR (heart rate), SBP (systolic blood pressure), W/U (work up), CVP (central venous pressure, ECHO (echocardiogram), PAC (pulmonary artery catheter), CI (cardiac index – L/min per m^2), PCWP (pulmonary capillary wedge pressure – mmHg), SV_{O2} (saturation of hemoglobin with O_2 in venous blood), SVRI (systemic vascular resistance), RVEDVI (right-ventricular end-diastolic volume index)

Choice of Resuscitation Fluids

"The Advanced Trauma Life Support (ATLS) protocol of the American College of Surgeons recommends the liberal use of isotonic crystalloid to correct hypotension in bleeding trauma patients" [12]. However, published data neither supports nor rejects this recommendation. While the liberal administration of fluids may increase blood pressure, it may also increase the bleeding. In some cases, the administration of crystalloids can result in anasarca, an accumulation of fluid in the peripheral tissues. If this occurs, colloids (typically albumin) can be used as resuscitation fluids. The data is inconsistent, but there is evidence that albumin can harm a subgroup of trauma patients, while it may have helped a subgroup of septic patients. Red blood cells, platelets, and plasma are also administered, but they are not necessary if the patient's hematocrit is greater than 30.

Chapter 5: Interview Results

While the strengths and weaknesses of the current shock monitoring technologies are described in the literature, the perceptions of clinicians and scientists are best gathered through in-person conversations. The interviews provide an opportunity to translate the limitations of the current technologies into a better understanding of the clinical need for improved shock monitoring. By speaking with clinicians about their challenges, companies can learn how to better position their products for market adoption.

What is Shock?

Clinicians are in general agreement about the definition of shock. Shock is a clinical state including hypotension and persistent, insufficient tissue oxygenation. It is broadly defined and can result from many different diseases and injuries. In all cases, vasodilation (low systemic vascular resistance), problems with the pumping function of the heart, or a low volume of circulating blood cause a patient to develop the clinical signs of shock. However, there is not a universal threshold for changes in any of these parameters that will result in shock. In fact, the body is able to compensate for many of the causes of low blood pressure, maintaining adequate tissue oxygenation. Today, clinicians use a systolic blood pressure of less than 90 mmHg as the threshold for shock.

Who is at Risk?

Shock describes a set of symptoms rather than an underlying condition. The importance of this becomes very clear when clinicians describe the types of patients that are at risk of going into shock. These patients include everyone in the operating room and intensive care unit, all trauma patients, and anyone with sepsis, anaphylaxis, spinal cord injury, liver disease, kidney disease, or heart disease. While shock can be broken down into different types that describe the mechanism (hypovolemic, cardiogenic, distributive), it is often difficult to determine which type of shock a patient is developing or at risk of developing since the signs and symptoms are similar.

In the OR, there is a reluctance to diagnose a patient as going into shock. One clinician explained that there is a medical liability associated with a particular diagnosis and the patient's subsequent outcome. Another clinician explained that a diagnosis of shock is not very meaningful because it does not describe the underlying mechanism of disease. And finally, since a diagnosis is not necessary to write an order for fluid, clinicians often begin treatment for patients that are going into shock before formally diagnosing them.

Clinicians consider a number of factors when determining a patient's risk of developing shock. The body's natural resistance to shock is determined by the patient's age and general health status. The magnitude of initial insult and complexity of surgical procedures are also important considerations. For example, a patient with acute appendicitis is not likely to go into shock provided that he or she arrives at the hospital within a short period of time. However, a patient with a perforated appendix has a higher risk of going into shock because of the increased inflammation throughout the body. And an 80 year old patient with a perforated appendix for two days has a very high risk of going into shock. Clinicians must assess the health risks of each patient and adjust the subsequent monitoring and management to reflect these risks.

While a clinician may be hesitant to diagnose a patient that is going into shock, there are Diagnosis Related Groups (DRGs) for shock. Diagnosis Related Groups are used by the Centers for Medicare and Medicaid Services (CMS) to classify hospital cases into categories based on their expected hospital resource use. DRGs are also used to determine how much CMS will pay the hospital for each patient. DRG 785.51 is the code for cardiogenic shock and 785.59 is the code for other shock without mention of trauma. There are also Medicare Severity-Diagnosis Related Groups (MS-DRG). These codes are categorized to indicate if there is a Major Complication/Comorbidity (MCC), a Complication/Comorbidity (CC), or a Non-Complication/Comorbidity. Additional factors complicate the coding and reimbursement that a hospital will receive. For example, effective 10/1/08, Medicare will not reimburse for a higher-paying DRG that is the result of complications or comorbidities that are hospital-acquired and preventable

[10]. It is likely that this policy change will decrease the number of patients that are diagnosed as going into shock, especially when the condition is believed to be transient.

How are Shock Patients Managed?

The management of shock patients primarily occurs in the emergency room, the operating room, and the intensive care unit, but for some patients, it can begin in the ambulance. For trauma patients, the early management that occurs in the ambulance and ER is the most critical predictor of the patient's outcome. The time sensitive nature of shock management led to the concept of the "Golden Hour" [37]. In some cases, the patient's outcome is determined before he or she arrives at the hospital.

The management of a shock patient depends, in part, on the natural history of the patient's underlying disease or injury. For example, if a patient arrives at the emergency room in shock, the clinician will focus on resolving the underlying injury or disease, providing only enough supportive care to delay the tissue injury that would result from inadequate perfusion. Once the source of the patient's injury has been resolved, the clinician will focus on resuscitation. In the operating room and the intensive care unit, clinicians have access to extensive monitoring technologies, so a decline in the patient's status can be detected quickly. In theory, this enables the clinician to intervene before the patient enters the advanced stages of shock.

What are the Current Monitoring Technologies and How are they Used?

Most monitoring technologies measure general vital signs rather than specific shock parameters. While there are many technologies that measure or estimate surrogates for blood flow and tissue health, no one surrogate provides a complete picture of tissue oxygenation. As a result, clinicians use several of the available monitoring technologies in combination. In the emergency room, the focus is on easy to use, non-invasive technologies that do not require complex configuration. Blood pressure, heart rate, and pulse oximetry are the most common monitoring technologies used in the ER. In the OR and ICU, more complex monitoring technologies can be used because there is more time

to insert and configure the monitors and the patient is typically in a more stable condition. The most common technologies that are used to monitor patients at risk of shock or being resuscitated from shock include:

- BP Cuff – cuff inflates every 4-5 minutes, measuring a patient's blood pressure
- EKG – continuously measures heart rate
- Arterial Catheter – blood gases (pH, lactate), continuous BP
- Foley Catheter – urine output
- Pulse Oximeter – pulse rate, % of bound hemoglobin (indicates oxygenation of arterial blood)

While the monitoring technologies listed above are the most common, there are other complementary technologies that can be used in higher risk patients. The Swan-Ganz or Pulmonary Artery Catheter is the most interesting of these technologies because until recently, it was widely used to monitor shock patients. The Swan-Ganz provides stroke volume, cardiac output, and mixed venous oxygen saturation, but its use is associated with substantial risks, including a risk of puncturing the artery or causing an arrhythmia. Additionally, the use of a Swan-Ganz catheter has not been shown to improve patient outcomes. There is also some data indicating that Swan-Ganz use has lead to doctors making the wrong clinical decisions [1]. For example, clinicians might be tempted to treat a low cardiac output when the low cardiac output is actually fine for a particular patient. While the Swan-Ganz provides clinicians with additional information, that information is only valuable if it leads to better patient management. Mixed venous saturation, a measure of how much oxygen is being extracted from the blood, is a surrogate for what is happening at the tissue level. Today, this parameter is only available to clinicians if they are using a Swan-Ganz catheter. However, Central Venous Catheters provide a means of continuously measuring the superior vena cava oxygen saturation, which is a surrogate marker of mixed venous oxygen saturation. Central venous catheters provide a less risky alternative for estimating tissue oxygenation.

There are other monitoring technologies that are only used when the clinician is concerned about the pumping function of the patient's heart. The transesophageal

echocardiogram provides two-dimensional views of the patient's heart, so the clinician can observe the filling and pumping functions. It can be used when the heart is at risk and a pulmonary artery catheter is contraindicated. It is often used during open heart surgery. The transesophageal Doppler measures blood flow through the aorta, so it can be used to estimate cardiac output.

What Parameters are Most Useful in the Management of Shock Patients?

Despite the vast array of complex monitoring technologies available, clinicians rely most heavily on their basic clinical tools and judgment. For example, several clinicians indicated that their eyes are their most valuable tool. The clinical examination of a patient, especially if the patient is awake and conscious, can provide a significant amount of information regarding the patient's status. In sepsis, a decline in mental status is often the first sign that a patient is going into shock. Pain, fever, skin turgor and pallor are also critically important. Blood pressure, heart rate, respiratory rate, and the percentage of bound hemoglobin provide the next level of information. These parameters are most valuable when they are observed in relation to one another and when trends from baseline can be observed. Urine output is probably just as important as the basic hemodynamic parameters because there is a threshold of urine production below which a patient is considered to be in trouble. And finally, clinicians discussed the value of the more invasive hemodynamic parameters, including lactate, pH, sodium bicarbonate, and central venous oxygen saturation. These parameters are believed to be better surrogates for tissue oxygenation than blood pressure, heart rate, and respiratory rate. While they were willing to discuss the most valuable parameters available through current monitoring technologies, several clinicians pointed out that there is no good technology for detecting organ hypoperfusion. Tissue oxygenation and tissue pH would be the ideal parameters for managing shock patients.

What are the Limitations of the Current Technologies?

According to the clinicians interviewed, there are three primary limitations of the current monitoring technologies. First, the current technologies measure or estimate surrogates

of blood flow rather than measuring tissue perfusion. As a result, clinicians do not know if their therapeutic interventions are helping the patient. They can increase blood pressure, but there is no indication that an increase in blood pressure translates to an increase in tissue perfusion. Second, the current technologies are not able to detect when the body's natural compensatory efforts are no longer sufficient. Clinicians are tempted to intervene early to prevent the patient from entering advanced shock, but these interventions do not take into account the body's natural ability to compensate for moderate hypoxia. And finally, most of the available technologies are invasive, non-continuous, and complex. Emergency room clinicians are the most concerned about the invasiveness and complexity of the current monitoring technologies because these limitations are deterring their use in the ER.

As a result of these limitations, clinicians make treatment decisions based on incomplete information. Interviewees suggested that there is a tendency to over-treat rather than waiting to determine if the body will be able to compensate, yet there is limited data available to assess whether the benefits of over-treatment outweigh the risks.

What are the Therapeutic Interventions?

Clinicians are challenged to determine when to intervene therapeutically. In theory, clinicians should intervene when the patient's body is no longer able to compensate for a particular insult and the body's tissues start to become hypoxic. However, the cruder the monitoring technology, the more likely a clinician is to intervene at the wrong time. Additionally, each patient's threshold for a particular parameter depends on the patient's age, genetics, and general health status. To further complicate the therapeutic intervention, the clinician must balance the need to treat the underlying disease or injury with the need to support the delivery of oxygen to the body's tissues.

Clinicians typically treat shock patients with crystalloid or colloid solutions if the patient is believed to be hypovolemic, and with vasoconstrictive drugs if the patient is believed to have low systemic vascular resistance. However, the underlying mechanism is not

always understood and it is generally believed that it is safer to administer fluid than vasoconstrictive drugs. As a result, clinicians typically give a small amount of fluid initially and wait to see how the patient responds before providing additional interventions. Crystalloid is administered first and it is sufficient in most patients. Colloid is sometimes administered if the patient becomes edematous because studies have indicated that colloid is retained in the circulation while crystalloid solutions leak out of the capillaries and into the interstitial space [12]. Clinicians typically give the patient fluid until it is no longer effective or until the patient's central venous pressure rises or there is a clinical response. If there is no response, or the response is not sufficient, clinicians may add a vasopressor. Several clinicians mentioned the concept of "filling the tank before you squeeze." This refers to giving fluid before administering vasopressors. This is important because vasoconstricting a patient who is hypovolemic can lead to increased tissue injury by making it even more difficult for the body to pump blood to the peripheral tissues.

In distributive shock, the blood vessels are dilated, which results in low systemic vascular resistance. This vasodilation results in a significantly larger volume of distribution, on the order of 30L as compared to 5L for a healthy patient. Not surprisingly, the "normal" volume of circulating blood is not sufficient to oxygenate the body's tissues in a vasodilated patient. Early fluid resuscitation is extremely important for these patients, but understanding the cause of the vasodilation is also important. In sepsis, finding the source of the infection can be a significant challenge. Clinicians describe the treatment of septic shock by breaking it into therapeutic emergencies and diagnostic dilemmas. In a therapeutic emergency, the clinician must drain the abscess and administer broad spectrum antibiotics before the organism has been identified. Once the organism has been cultured, the antibiotics can be adjusted to better target the infection. If the patient is not in immediate danger, the clinician can culture the organism before choosing the appropriate antibiotic.

In hypovolemic shock, the patient has lost blood, but the pumping function of the heart is normal and the volume of distribution is normal. The source of the blood loss must be

identified and resolved before the clinician can administer large quantities of fluid. In the early management, clinicians administer just enough fluid to stop the decline of the patient's status and hopefully prevent damage to the tissues. In most cases of hemorrhagic shock, vasopressors are not helpful because the patient is already in a vasoconstricted state. Rather, clinicians administer fluid and anesthesia, which has the effect of vasodilating the patient. The goal is to move the patient from a state of low blood pressure and vasoconstriction to a state of low blood pressure and vasodilation. This facilitates the delivery of oxygen to all of the body's tissues rather than only preserving the blood flow to the central organs. Once the source of the bleeding has been resolved, the clinician can increase the fluid administration, which should bring the blood pressure back into the normal range.

In cardiogenic shock, fluid should not be administered because it will overload an already weakened heart. In a person with a compromised heart, additional fluid can lead to congestive heart failure. In practice, this is extremely rare because clinicians typically administer fluid slowly and make sure the patient is responding favorably before administering more fluid. The treatment for cardiogenic shock focuses on resolving the cardiovascular injury. This might involve performing minimally invasive surgery like angioplasty to open a blood vessel, conducting open heart surgery to repair a defect, or administering therapies designed to increase the pumping function of the heart.

During fluid resuscitation, clinicians must determine when to administer crystalloids or colloids and when to administer blood products. The maximum allowable blood loss can be calculated for a particular patient to ensure that hemoglobin and hematocrit levels remain above an appropriate threshold. Hematocrit can drop to about 7 or 8 and hemoglobin can drop to about 3 or 4 without causing secondary tissue injury. However, clinicians typically administer blood products when the hematocrit drops below 30. For actively bleeding patients, protocols are in place to provide a standard approach to fluid resuscitation. If a patient is actively bleeding, clinicians give a 6:6:1 ratio of red cells to plasma to platelets.

The most common endpoints of resuscitation are identical to the most useful parameters for diagnosing shock. These parameters include blood pressure, heart rate, lactate, and pH. About two thirds of bleeding patients have a low blood pressure and a high heart rate. If a patient's blood pressure improves in response to fluid resuscitation, it usually means that the bleeding has stopped. If the blood pressure gets worse or stays the same, it usually means that the patient is still bleeding. Base deficit and pH provide an instantaneous state of shock while lactate indicates how long and how severely a patient is in shock. Lactate is currently the gold standard for resuscitation, but a change in the negative trend of any of these parameters typically indicates an improvement in the patient's shock status.

What Goes Wrong?

The most significant problems that occur while monitoring and managing shock patients are the result of a misdiagnosis, a misinterpretation of the data, or some other form of mismanagement. These problems can lead to the wrong clinical decisions. For example, problems with cardiac function can be missed and unsuspected volume loss can accumulate in the retroperitoneum, the abdomen, the chest, or the pelvis. Additionally clinicians can be misled by what appears to be normal vital signs. Since the current monitors measure surrogates, normal values can disguise an underlying pathology. For example, young, healthy people have strong compensatory mechanisms designed to protect the critical organs during a loss in circulating volume. These compensatory mechanisms can preserve "normal" vitals, including blood pressure and heart rate, even when the patient has lost or is continuing to lose significant amounts of blood.

In addition to the challenges of monitoring and managing shock patients, clinicians also worry about the natural history of the underlying disease or injury. In patients with hemorrhage, clinicians are not always able to control the bleeding. Treatment of septic shock relies on the resolution of the underlying infection, which in turn depends on the age and health of the patient and the characteristics of the bacteria. If a patient is in shock when he or she arrives at the emergency room, the patient's outcome may have

already been determined. The clinicians provide supportive care while attempting to resolve the underlying injury. The goal of the supportive care is to avoid additional damage, allowing the body to recover, but recovery is not always possible. If the patient has been in shock for too long, critical organs such as the brain, heart, kidneys, liver, or gut, may have been without oxygen for too long. In these cases, the patient can experience multiple organ failure and die.

Problems can also occur after the clinician resolves the underlying condition and resuscitates the patient. Systemic Inflammatory Response Syndrome (SIRS) can develop in trauma and sepsis patients. In SIRS, patients lose fluid from the central circulation to the periphery because the capillaries become leaky. SIRS has a 50% mortality rate and no one knows how to treat it. Even if SIRS is avoided, a patient can develop organ failure several days after being fully resuscitated. The mechanism is not clear, but it is likely that the organs suffered more hypoxia than they could withstand.

How has the Management of Shock Patients Changed Over Time?

The management of shock patients has changed significantly over time. Interviewees described these developments as changes in the approach to shock management, changes in monitoring technologies, and changes in therapeutic interventions.

Approach to Shock Management

Clinicians now have a better understanding of the mechanisms of shock and the mechanisms of the patient's underlying disease or injury. They have learned that an increase in tissue oxygenation, not a particular blood pressure or heart rate, should be the goal in shock management. Ten years ago, if a patient's blood pressure was low, the clinician would administer fluid and a vasoconstrictor until the blood pressure returned to normal. However, this often resulted in extreme edema and it sometimes resulted in ischemic peripheral tissues that would require amputation. Now, clinicians administer a smaller amount of fluid, keeping patients relatively dry; a vasoconstrictor is not administered until after the patient has received fluid. The pendulum is swinging, but

both approaches are probably over-reactions. In trauma, clinicians now give the body time to compensate for the injury by vasoconstricting and clotting. Administering fluid dilutes the blood, making it more difficult for the body to perform these important compensatory functions. For this reason, clinicians try to keep the composition of the blood as close to physiologically normal as possible. To do this, they follow a 6:6:1 protocol that recommends the administration of equal amounts of red blood cells and plasma and the occasional administration of platelets.

Significant improvements have been made in treating the end stages of shock. Mortality in the ICU is still as high as 80%, but patients are rarely dying from the late complications of shock. However, very little has changed in the early management of shock. The biggest change involves the role of the paramedic. Paramedics used to "stay and play," performing limited interventions to stabilize the patient. Now, paramedics are instructed to "load and run," minimizing the time it takes to transport a patient to the emergency room [14]. This is another pendulum swinging from one extreme to the other and it is likely that the ideal approach would fall somewhere in the middle. Despite all of the changes, clinicians still struggle with the challenge of identifying the root cause of shock, especially in sepsis, and balancing source control with resuscitation.

Monitoring Technologies

In the medical community, it is common for technologies to go in and out of favor as clinical experience accumulates. Ten years ago, there was some interest in capnography, a monitoring technology that measures the concentration or partial pressure of carbon dioxide in the respiratory gases and provides an indirect measure of cardiac output. The device was fairly reliable, but extremely cumbersome to insert. As a result, it is no longer used. The Swan-Ganz or pulmonary artery catheter is another technology that has gone out of favor over the last few years. Data emerged that questions the impact of the Swan-Ganz catheter on patient outcomes. Since there are also risks associated with the insertion of a pulmonary artery catheter, its use has declined significantly over the least few years.

There are several promising new technologies that could have a significant impact on the monitoring and management of shock patients. For example, the transesophageal echocardiogram allows clinicians to observe the pumping function of the heart. This provides an approximation of cardiac output, but it does not completely replace the data available from a pulmonary artery catheter. Arterial waveform is also being used to calculate cardiac output, primarily in patients with cardiogenic shock. Clinicians now have more options for minimally invasive and non-invasive testing of hemodynamic variables. There are more blood tests, including pH, lactate, and triponin, and point-of-care analytical devices provide a means of testing the patient's blood at the bedside. This bedside testing is not widely used, but it could increase the utility of blood gases in the management of shock patients. There are also new technologies, including near infrared spectroscopy and thermal diffusion, designed to provide information about what is happening at the tissue level. While clinicians would value this tissue information, the technologies are still unproven and the interviewees wonder if they will have an impact on patient outcomes.

Therapeutic Interventions

The therapies that clinicians use to treat shock patients have changed very little. For patients with hemorrhage, there are new products available to help patients clot. With regards to vasopressors, dopamine is no longer used and vasopressin is now the vasopressor of choice. While the therapies have not changed significantly, the ways in which clinicians use the therapies has changed. I have discussed these changes in the Approach to Shock Management section.

Overall Satisfaction

I asked each clinician to rate their satisfaction with the technologies available for monitoring shock patients. Several clinicians are reasonably satisfied with the monitoring of patients that are at risk of shock, but the majority of clinicians interviewed

are extremely dissatisfied. In contrast, there is a wide range of satisfaction levels with the monitoring of patients that are being resuscitated from shock.

In monitoring patients at risk of shock, the mean satisfaction level is 2.9 out of 7 and the standard deviation is 1.1. For patients that are being resuscitated from shock, the mean satisfaction level is 3.6 out of 7 and the standard deviation is 1.6. While the means and standard deviations are fairly similar, the distribution of responses indicates that there are important differences in the monitoring of these patient populations.
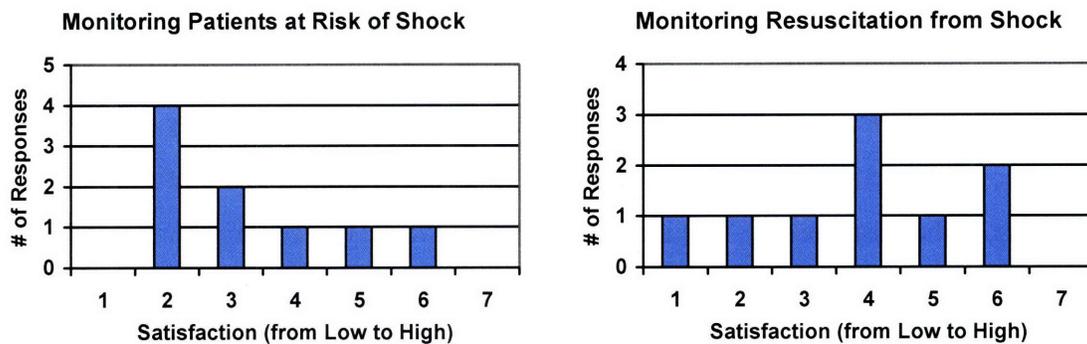
One of the clinicians stated that if you understand physiology, you only need the measurements of blood pressure, heart rate, and blood gases (via an arterial line) to manage shock patients. This opinion differs significantly from the opinions of several other clinicians who stated that the sensitivity and specificity of the current technologies is extremely low, making the technologies insufficient. While sensitivity and specificity are both important, the sensitivity of the monitoring technologies is of particular importance in the monitoring of patients that are at risk of going into shock because the risks associated with not resuscitating a patient that is going into shock (false negatives) far outweigh the risks associated with resuscitating a patient that is not going into shock (false positives).

There are several reasonable explanations for why clinicians are more satisfied with the monitoring of patients that are being resuscitated from shock. The clinician already knows that there is a problem, so there is not a risk of missing the patient's declining

health status. However, while the clinician may know that the patient went into shock, it may not be clear if the patient has been sufficiently resuscitated from shock. For this reason, the specificity of the technology is critically important when monitoring patients that are being resuscitated from shock. Another possible explanation for the higher satisfaction level is that there are well developed protocols for resuscitation that are widely used by clinicians, so the clinician's response to a patient in shock is standardized. It is also worth noting that clinicians' satisfaction with the current technologies could be due to the fact that they do not miss what they do not have. Finally, I should acknowledge that I spoke with clinicians at some of the country's leading hospitals. One of the interviewees explained that he has access to almost any technology he wants because he works at a premier hospital. These hospitals and clinicians have access to more advanced technology than clinicians at a majority of the nation's hospitals.

What is the Biggest Challenge in Monitoring and Treating Shock Patients?

Several clinicians discussed the challenge of discovering the underlying cause of a patient's hypotension and hypoperfusion, especially in rapidly declining patients. In many cases, clinicians do not know if a patient's low blood pressure is a serious problem. Since there are not good surrogates for measuring the hypoxia of local tissue beds, they do not know what is happening at a cellular level in different parts of the body. This makes it extremely difficult for a clinician to know when to stop an intervention or when to change directions. In some cases, clinicians retreat into a "cover your ass" mentality or a "are we practicing within the standard of care" mentality rather than tailoring their interventions to address the perceived needs of a particular patient. In the emergency room, clinicians have additional challenges. If a patient arrives at the ER in shock, the clinician has very little time to intervene and sometimes it is already too late. One clinician summarized the challenges of monitoring shock patients by stating that the current technologies are too invasive and complex, not continuous, and do not provide an accurate indication of the patient's status.

Desired Improvements in Monitoring

Even though some clinicians are fairly satisfied with the current monitoring technologies, all of the clinicians are looking for improvements. When I asked if an earlier warning would change the patient's outcome, I learned that an earlier warning is less important that an accurate warning. In shock monitoring, an accurate warning would alert clinicians that the patient's compensatory system is no longer able to perfuse the body's tissues and it would also let clinicians know when a patient has been sufficiently resuscitated. Therefore, the monitoring technology would need to be more sensitive and specific than the currently available technologies. Since the risk associated with resuscitating a patient that is not going into shock is lower than the risk associated with not resuscitating a patient that is going into shock, false positives can be tolerated, while false negatives are unacceptable.

One of the limitations of the current monitoring technologies is that the currently available surrogates are not very sensitive or specific to shock. It would be extremely valuable for a clinician to be able to accurately monitor tissue oxygenation. This would help clinicians to determine when to begin or end treatment and it might help to determine the underlying cause of the shock state. It should be noted that while an earlier, more accurate warning would be valuable, it is difficult to quantify how much earlier or more accurate would be necessary to alter a particular outcome because the outcome generally depends on the underlying disease process.

Not surprisingly, several desired improvements differ depending on the environment where the patient is being monitored and treated. In the ER, clinicians typically rely on blood pressure, heart rate, and pulse oximetry because more invasive monitoring technologies take time to insert and the resulting data do not provide enough incremental benefit to justify the required time. In the ambulance, paramedics do limited monitoring and rarely intervene because of evidence that these interventions do not improve outcomes [12]. ER and ambulatory clinicians are looking for non-invasive monitoring technologies that are quick and easy to calibrate and provide continuous feedback to help the clinicians determine the status of a patient and if a particular intervention is working.

In the OR and the ICU, clinicians generally use more extensive monitoring technologies, but tissue oxygenation and perfusion data are not available. A combination of the Swan-Ganz catheter or a central venous catheter, pH, and lactate provide the closest estimate to tissue oxygenation. Less invasive monitoring of the current parameters would be useful, but a more sensitive and specific marker of tissue injury would be much more valuable.

Value of a Tissue Perfusion Monitor

I ended the interviews by asking clinicians to rate the value of a real-time, continuous, tissue perfusion monitoring device in the management of shock patients. The overwhelming consensus is that this type of technology would be extremely valuable. In fact, for patients at risk of shock and patients being resuscitated from shock, the value of a tissue perfusion monitoring was given a mean rating of 6 out of a possible 7, with a standard deviation of 1.1.
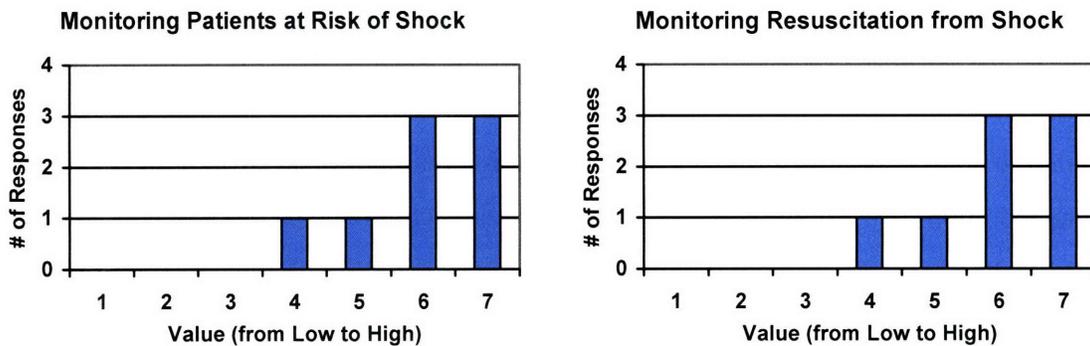
A continuous, real-time tissue perfusion monitor would be valuable for patients that are at risk of shock and for patients that are being resuscitated from shock. For patients who are not in shock or progressing towards shock, it would be useful to know that their tissues are not in danger. A tissue perfusion monitor would also allow clinicians to provide more precise resuscitation. One clinician gave me a recent example of a patient who would have benefited from a tissue perfusion monitor. A young man, in his 20's, was stabbed multiple times in the chest and neck. His heart, carotid artery, and saphenous vein were punctured. The paramedics transported him to the emergency room,

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reporting that he had lost vital signs at the scene and had likely been without vital signs for about 15 minutes. The emergency room clinicians believed that the patient would be brain-dead and as a result, a majority of the team did not support the resuscitation of this patient. While the clinician who I interviewed agreed that the patient could not be saved, he believed that resuscitation was warranted because the patient's organs could be donated to other patients, thereby saving several lives. The patient underwent extensive surgery and resuscitation before being brought to the ICU. When the clinician returned to the ICU the next day to check on the patient's status, he touched the patient's shoulder and the patient opened his eyes. The patient fully recovered from his injuries with no permanent brain damage or other tissue injury. The clinician who I interviewed believes that an accurate tissue perfusion monitor would have alerted the clinicians that the patient's tissues were still viable and the decision to resuscitate him would not have been challenged. In this particular case, the outcome would not have changed, but if the patient had been older, or if it had been a different clinician, the team might not have attempted resuscitation and the patient could have lost his life.

Criteria for a Tissue Perfusion Monitor

While the clinicians agreed that a tissue perfusion monitor would be valuable, they each expanded upon their rating by stating that the device would need to meet a number of additional criteria. First, it would need to measure the perfusion of one or multiple tissue beds that are relevant to the shock condition. Second, the tissue perfusion monitor would need to be more sensitive and specific than the current monitoring technologies. Third, it would need to be clinically relevant and easy to use. Finally, the device would need to be flexible enough to be used for a variety of different patients and in a variety of different environments.

There is consensus that a tissue perfusion monitor would need to measure the perfusion of a meaningful tissue. The brain, heart, kidney, and gut were mentioned by several clinicians. These tissues are believed to be much better markers for shock than the skin or muscle. One clinician stated that a tissue perfusion monitor would be most useful in

cases where there is a specific organ that is at risk. For example, perfusion of the kidney would be extremely helpful in predicting renal failure after a complex surgery. While it might be possible to identify one relevant tissue bed, some clinicians believe that the perfusion of multiple tissue beds would be necessary to detect when the body's autoregulation is no longer sufficient.

The tissue perfusion monitor would need to be more sensitive and specific than the current monitoring technologies, providing better feedback to clinicians. Today, clinicians rely on blood pressure, heart rate, blood gases, and urine output to indicate if a patient is responding to a therapeutic intervention. These parameters are not sensitive or specific to shock.

A tissue perfusion monitor would need to be easy to use, providing both an absolute value and trends, and it would need to provide a clinically meaningful value in order for clinicians to be willing to adopt the technology. To be clinically meaningful, the tissue perfusion monitor needs to display the perfusion in units that the clinician can understand. The clinicians also stated that the monitor would need to have well-established thresholds to indicate when a patient is in danger or when a patient has been sufficiently resuscitated. A non-invasive monitor would be the most useful, but clinicians stated that a minimally invasive technology could be successful if the information was shown to be extremely valuable.

Finally, the tissue perfusion monitor would need to work in a variety of different situations and environments. For example, it would need to function for obese or edematous patients and when the patient's autoregulatory system is vasoconstricting flow away from the periphery. It would also need to function in the emergency room, in the operating room, and in the intensive care unit, and it would ideally be able to travel with the patient, so that trends could be captured for the patient's entire time in the hospital.

At the end of the day, the utility of a tissue perfusion monitor needs to be supported by outcome data in animal models or humans.

Chapter 6: Implications

The literature and interviews validate the need for better shock monitoring technologies. However, to ensure adoption, new technologies will need to address the limitations of the current monitoring technologies.

Clinical Factors

Sensitivity and specificity, clinical relevance, and ease-of-use are critical factors that will drive market adoption.

- **Sensitivity and Specificity:** The currently available technologies are not sensitive or specific to shock. Rather, they measure systemic parameters that are believed to roughly correlate with tissue perfusion and oxygenation. While sensitivity and specificity are both important, their relative importance depends whether the patient is at risk of shock or being resuscitated from shock. Sensitivity is more important in the diagnosis of shock because the risks associated with not diagnosing a patient that is going into shock far outweigh the risks associated with resuscitating a patient that is not going into shock. Specificity is more important in the resuscitation from shock because the clinician needs to be absolutely certain that the patient has been sufficiently resuscitated from shock. An improved shock monitoring technology will be more sensitive and specific, accurately detecting when a patient is going into shock and when a patient has been sufficiently resuscitated from shock.

- **Clinical Relevance:** In the context of shock monitoring technologies, clinical relevance has several meanings, but the ultimate goal is to improve patient outcomes. An improved shock monitoring technology should measure a parameter that the clinician understands physiologically. The measurement should be absolute and it should be provided in units that are meaningful. And finally, the parameter should have thresholds that are fairly consistent across a diverse patient population. Ideally, an improved shock monitoring technology

would measure the instantaneous state of tissue perfusion or tissue oxygenation as well as the cumulative oxygen deficit.

- **Ease-of-Use:** With so many available monitoring technologies, ease-of-use is an important consideration. Non-invasive technologies are preferable, but a minimally invasive technology will be adopted if it provides information that is superior to the information available from the current technologies. In addition to invasiveness, the set-up and configuration requirements are critical to the success of a new monitoring technology. Several technologies, including gastric tonometry, failed to receive widespread adoption because of the time required to insert and configure the device.

While each of these characteristics are important, their relative importance differs depending on the clinical setting in which the device will be used. For example, in the emergency room and ambulance, ease of use is extremely important because patients are being moved around for multiple tests and clinicians do not have time to wait for a device to calibrate. In contrast, patients in the operating room and intensive care unit are not being moved and there is generally more time to insert and calibrate a device. There is also a higher tolerance for invasive monitoring technologies in the operating room and intensive care unit.

Market Factors

The dynamics of the patient monitoring market will play an important role in driving adoption of a new monitoring technology. In the multiparameter patient monitoring market, there is a trend towards telemetry and central monitoring [9]. These enhancements make it easier for clinicians to monitor multiple patients simultaneously. An improved shock monitoring technology will be more widely adopted if it can be integrated into an existing monitoring platform. There are several benefits to the development of a module, versus a stand-alone monitoring technology. For example, if a hospital does not need to purchase additional capital equipment, the purchasing decision will be much easier. Additionally, clinicians would appreciate a reduction in the wires

and devices that surround a patient. And finally, as hospitals standardize their monitoring technologies to optimize training and enhance continuity of care, they will be inclined to choose technology platforms that can incorporate many different monitoring parameters.

Companies interested in entering the patient monitoring market should consider partnering with one of the existing players. Philips Medical Systems and GE Healthcare are the leading players, representing over 70% of the hospital vitals signs patient monitoring market [9]. Appendix B contains a list of patient monitoring companies and their respective product lines.

Clinical Trial Design

Companies must design clinical trials that will enable them to demonstrate clinical utility in the crowded shock monitoring market. They must choose the type(s) of shock, the clinical environment, the comparative parameter(s), and whether to target their trial at the diagnosis of shock or the resuscitation from shock. As a company considers the most appropriate clinical trial design, ethical issues, such as obtaining informed consent, are also important.

Type of Shock

Hypovolemic shock is the most common type of shock and the mechanism is well understood. Distributive shock is also quite common, but the underlying mechanism and natural history are more complex. This complexity could make it more difficult to demonstrate an improvement in shock monitoring. Since cardiogenic shock is caused by a cardiac defect that prevents the heart from pumping sufficiently, the current technologies that measure cardiac output or provide images of the heart are probably sufficient.

Clinical Environment

The challenges and opportunities associated with shock monitoring differ depending on the environment where the monitoring occurs. For example, there might be a lower bar for demonstrating the utility of a monitoring technology in the emergency room than in the intensive care unit because fewer monitoring technologies are used in the emergency room. However, the challenges associated with the design of a randomized controlled trial, including the challenge of informed consent, in the emergency room make a trial in this environment impractical [5]. To increase the probability of success, companies should conduct their clinical trials in the clinical environment with the lowest risk profile.

Comparative Parameters

Since there is not a perfect surrogate for shock, companies should consider comparing new monitoring technologies to several of the parameters that are measured by the currently available technologies. Companies should choose comparative parameters that are widely used and believed to be reasonable surrogates for tissue perfusion and oxygenation, such as mixed venous oxygen saturation, pH, and lactate. While companies will eventually hope to establish superiority over the current monitoring technologies, non-inferiority trials will need to be completed first. If the monitoring technology is less invasive or easier to use than the comparator technology, favorable results from a non-inferiority trial could be sufficient to drive market adoption.

Diagnosis or Resuscitation?

There is a clinical need for improved technologies to monitor patients that are at risk of going into shock and patients that are being resuscitated from shock. Today, many of the same technologies are used for both patient populations. However, companies should choose the most appropriate patient population for conducting a clinical trial. If the trial were designed to diagnose shock patients, it would require an extremely large patient population because only a small percent of the patients would ultimately go into shock. However, if the trial were designed to monitor the resuscitation of shock patients, a smaller patient population would be sufficient to demonstrate the benefits of the new

monitoring technology. The sensitivity and specificity of the new technology should also guide the selection of an appropriate patient population because sensitivity is more important for the diagnosis of shock and specificity is more important for the monitoring of resuscitation from shock.

Recommendation

The interviews and research highlight several important factors that can guide the clinical trial design for new shock monitoring technologies. Hypovolemic shock is the most logical choice for a clinical trial because it is the most common form of shock and the mechanism is well understood. To minimize the risks associated with the clinical environment, companies should conduct their trials in the intensive care unit, where clinicians have the time to conduct extensive monitoring. Since there is not one ideal surrogate marker for shock, companies should choose comparative parameters that are widely used and believed to be reasonable surrogates for tissue perfusion and oxygenation. Mixed venous oxygen saturation or central venous oxygen saturation, lactate, and pH are the most logical choices because these parameters are believed to provide the closest approximation to what is happening at the tissue level. However, for completeness, it would also be useful to correlate the findings with systemic parameters, such as heart rate and blood pressure. And finally, based on the cost and time requirements, companies should design their clinical trials to monitor the resuscitation of shock patients.

Chapter 7: Summary

Conclusions

The goal of this research was to characterize the current shock monitoring and management techniques and to analyze the need for an improved shock monitoring technology. In order to better ascertain if the current monitoring technologies are adequate, I defined the standard of care for monitoring patients that are at risk of going into shock and for monitoring patients that are being resuscitated from shock.

I developed a hypothesis that the limitations of current monitoring technologies contribute to the high mortality rate associated with shock. To empirically assess my hypothesis, I conducted an extensive review of the scientific literature and I interviewed nine clinicians and three scientists. The scientific literature identified the challenges of preventing and managing shock and described the currently available monitoring technologies. The interviews were particularly insightful because they highlighted the clinicians' perceptions about the monitoring technologies and provided me with an understanding of how the current technologies are used in combination with each other. The interviews also alerted me to the other non-monitoring challenges that are associated with the management of shock patients.

Despite the large number of technologies available to monitor patients, shock continues to be a life threatening condition. While there are several factors driving the high mortality rate from shock, this research confirms my hypothesis that the limitations of the current shock monitoring technologies play a significant role.

There is a clinical need for improved shock monitoring technologies. However, for a new technology to attain market adoption, it will need to address and overcome the limitations of the current technologies. A monitoring technology is only valuable if it enables clinicians to better manage patients and improve outcomes. Very few of the current shock monitoring technologies have been able to consistently demonstrate

improved patient outcomes. In the case of shock monitoring, clinicians believe that the measurement of regional tissue perfusion or oxygenation would more accurately predict when a patient is going into shock or when a patient has been sufficiently resuscitated from shock.

Limitations

My thesis research demonstrates that there is need for improved shock monitoring technologies. However, there are limitations to my research that must be acknowledged. The biggest limitation is the small number of interviews that I conducted with clinicians and scientists. A more comprehensive analysis would have included a large number of clinicians who work in each clinical environment and it would have included clinicians working at community hospitals in addition to academic medical centers. Another limitation is the interview guide itself. Since I conducted one hour interviews, I was limited in the number of questions that I could ask the clinicians. A longer interview, with more detailed questions, would have provided additional insights for a company interested in launching a new monitoring technology. For example, I would have asked questions about clinical trial design and the data clinicians would need to see before deciding to purchase and use the device. I also would have asked questions about the clinicians' willingness to pay for an improved shock monitoring technology. And finally, while I conducted extensive background research, I was not able to read every publication relevant to shock monitoring and management. As a result, I may have inadvertently excluded information that is relevant to a company's decision to enter this market.

Future Research

While the interviews and research provide insights that can guide the clinical trial design, additional data is needed to validate the recommendations and the needs of the market.

Clinical Need

What patients would benefit the most from an improved shock monitoring technology? What clinical trial endpoints are necessary to demonstrate clinical utility for these patients?

The Army Institute for Surgical Research has a Trauma Vitals Program that collects data on trauma patients transported to the emergency room by helicopter. Nurses correlate this data with the outcomes in the hospital. This group is also creating a database with the vital signs of healthy volunteers subjected to a negative pressure chamber. These databases would be helpful in validating where the clinical need is the greatest. Additional data may be available from the Society of Critical Care Medicine or the Institute of Critical Care Medicine.

Market Opportunity

What are the economics of shock monitoring and management? Do the economics vary depending on the type of shock or the clinical environment where the shock patients are being managed?

A follow-up survey might be necessary to clarify the interview results and better delineate how much the market is willing to pay for an improved shock monitoring technology. Based on the research and interviews, it is not clear how hospitals would value an improved shock monitor. It is also not clear if the value is the same for the different types of shock and the different clinical environments. Hospitals have committees that are responsible for assessing the need for new devices and approval by the committee is necessary before clinicians are permitted to purchase and use a new device. This can pose a significant challenge for a company interested in penetrating the hospital market because committee approval typically requires a Key Opinion Leader within the hospital to act as product champion. These product champions make the case for the device and shepherd the device through the process. Companies should not

underestimate the need for one or multiple product champions and should actively work to develop collaborative relationships with Key Opinion Leaders.

Appendix A: Interview Guide

Patients at Risk of Shock

- How do you define shock?
- What types of patients are at risk of going into sudden shock?
    - Can you break it down by the different types of shock?
    - What criteria are used to determine if a patient is at risk?
    - Of those at risk, what percent ultimately go into shock?
- How are patients that are at risk of shock managed?
    - Who makes the decision (physician, nurse, other)?
    - Where does this management occur (ER, OR, ICU, patient's room, etc.)?
    - What monitoring technologies are used and in what combination?
        - Does it vary depending on the type of shock a patient is at risk of?
    - What parameters are most useful in detecting when a patient is going into shock?
        - What provides the earliest indication?
        - Can you describe any limitations of these products?
    - When do you intervene?
        - What interventions are used for each type of shock?
        - How has this changed over time?
- What goes wrong and why?
    - What do you do and what's the outcome?
- Would an earlier warning of a patient's entry into shock change the management or outcome?
    - How much earlier would be necessary? How would the treatment or outcome change?
- In general, how has the management of patients at risk of going into shock changed over time?

Patients in Shock

- What criteria do you use to determine if a patient is in shock?
    - Does this vary based on the type of shock?
- How do you manage patients that are in shock?
    - How does it vary depending on the type of shock?
    - What monitoring technologies are used and for what purposes?
        - Can you describe any limitations of these technologies?
    - For what indications is fluid resuscitation appropriate?
        - What fluids are administered and in what situations?
        - How are the fluids administered? Protocol?
        - What endpoints are used to confirm adequate fluid resuscitation?
- What goes wrong and why?
    - What do you do and what's the outcome?
- Would an improved measurement of tissue perfusion change the management or outcome of patients that are in shock?
    - How would the treatment or outcome change?
- On a scale of 1-7, how satisfied are you with how you monitor and treat:
    - Patients at risk of going into shock?
    - Patients that are in shock?
- What is the biggest problem that you have in monitoring and treating these patients?
- Are you aware of any new technologies to improve monitoring of these patients?
    - What about technologies that were not successful?
- Can you rate on a scale of 1-7, the value of a real-time, continuous, and absolute tissue perfusion monitor for:
    - Monitoring patients at risk of going into shock?
    - Monitoring of patients in shock?
- Any other comments?

Appendix B: Patient Monitoring Companies

- Analogic
  - Products include digital radiography, fetal monitors, imaging subsystems, computed tomography, patient monitors, and airport security systems
- CAS Medical Systems
  - Products include patient monitoring, cerebral oximetry, mother/baby monitoring, blood pressure cuffs & supplies, and non-invasive blood pressure monitoring technology (for OEMs)
- Colin Medical Technology Corporation (an OMRON Company)
  - Products include portable vital sign monitors and multiparameter monitors
- Criticare Systems, Inc.
  - Products include pulse oximeters, vital signs monitors, anesthesia/OR monitors, and central station systems
- Datascope
  - Products include bedside and central monitors
- Draeger Medical
  - Products include anesthesia workstations, patient monitoring, central and bedside workstations, telemetry and wireless monitoring, jaundice management, ventilation, and warming therapy
- Fukuda Denshi
  - Products include electrocardiographs, bedside and central patient monitors, and ultrasound technology
- GE Healthcare
  - Products include a full line of patient monitoring systems
- Mennen Medical
  - Products include patient monitoring, radiology, hemodynamic monitoring, and non-invasive temperature management systems
- Mindray
  - Products include patient monitoring, anesthesia, diagnostic laboratory instruments, and ultrasound systems

- Nihon Kohden
  - Products include bedside and central monitors, pulse oximeter, SpO2/CO2 monitor, electroencephalograph, evoked potential/EMG system, hematology analyzer
- Phillips Medical Systems
  - Products include x-ray, ultrasound, MRI, computed tomography, nuclear medicine, information management, and resuscitation
- Schiller AG
  - Products include pulse oximetry and transport monitoring
- Spacelabs Healthcare
  - Products include patient monitors, anesthesia and ventilation, and diagnostic cardiology products
- Welch Allyn
  - Products include continuous patient monitoring and automated vitals signs capture

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