Study to Evaluate Adequate Resuscitation using Mixed Venous Oxygen Saturation in Response to a Short Duration Increase in Inspired Oxygen

Permalink
https://escholarship.org/uc/item/3wf2b8zp

Author
Novick, Noah S

Publication Date
1998-04-01

License
CC BY-NC-ND 4.0
Study to Evaluate Adequate Resuscitation using Mixed Venous Oxygen
Saturation in Response to a Short Duration Increase in Inspired Oxygen

by
Noah Solomon Novick
MBA Stanford University 1998
A.B. (double) Stanford University 1995

A thesis submitted in partial satisfaction of the requirements for the degree of Master of Science in Health and Medical Sciences in the GRADUATE DIVISION of the UNIVERSITY OF CALIFORNIA, BERKELEY

Committee in charge:
Professor John G. Forte, Chair
Professor Marian C. Diamond
Professor Terry E. Machen
Spring 1998
The thesis of Noah Solomon Novick is approved:

Chair: Dr. John G. Forte  
Department of Molecular and Cell Biology

Dr. Marian C. Diamond  
Department of Integrative Biology

Dr. Terry E. Machen  
Department of Molecular and Cell Biology

University of California at Berkeley

Spring 1998
I. INTRODUCTION

I. i. Background Information

To J. C. Marshall, multiple organ dysfunction syndrome (MODS) and its reversal is "the dominant paradigm of intensive care...more than just a syndrome." 

"MODS is more than a simple inventory of ICU technology or the process of death...It reflects the evolution of intensive care centered around the support of organ system function." This 'evolution' has been marked by a shift in the most common cause of mortality with, unfortunately, warfare being the primary driver for these changes as well as, ironically, for the advances that ensued. Consider, please, the account given by Richard Barton and Frank Cerra of the Department of Surgery at the Medical School, University of Minnesota.

"World War I led to the concepts of fracture immobilization and shock resuscitation. With World War II came blood banking and an emphasis on

---


2 ibid.
early evacuation and operative treatment of battlefield casualties. As early mortality rates from hemorrhage improved, survivors came to be at risk for late complication, and in the Korean War, acute renal failure became one of the leading causes of death. While early fluid resuscitation, with rapid evacuation and definitive operative treatment, reduced the incidence of acute renal failure, the Vietnam War introduced a new complication of shock, the adult respiratory distress syndrome (ARDS). Initially thought to be the result of overzealous fluid administration, it became clear that ARDS was actually a complication of circulatory shock, infection, and tissue injury in non lung areas of the body. By the mid 1970s it became increasingly clear that the pathophysiology of ARDS was not confined to the lung but is part of a systemic injury-response pattern now known as the hypermetabolism-organ failure syndrome.\(^3\)

Progress in severely acute and acute mortality in response to shock unmasked the more complex, subacute pathophysiologic process of the Hypermetabolism Multiple Organ Failure Syndrome. MODS "is probably best viewed as the clinical end stage of the systemic hypermetabolic response to injury that is heralded by acute lung injury, and followed by hepatic and renal failure.\(^4\)"

---


\(^4\) ibid.
MODS is by far the leading cause of death in the surgical ICU today. It accounts for 70% to 80% of deaths. The patients who pass away are often in the ICU for an extended period, perhaps three weeks in one case, perhaps five or two in another. At any rate, costs may easily rise several hundred thousand dollars for these patients. In survivors, rehabilitation may take months, with estimated additional costs easily in the range of $500,000 or more and sometimes in the millions.

Marshall argues that "since the ICU exists as a geographic locale for the support and monitoring of respiratory, cardiovascular, hepatic, and renal function, the need for this support is a compelling method of describing the...disease process evolving in the ICU, and conversely, the prolonged failure of support to restore normal physiologic function, justifies its [the support's] discontinuation." Therefore, predictive measures play an important role not only in research hoping to take steps toward greater understanding for treatment, but also for the important and complex socioeconomic issues that face ICUs today.

---

I. ii. Pathophysiology

As mentioned above, it is pulmonary dysfunction which usually first heralds the syndrome. The insult may be primary (lung contusion, pneumonia) or secondary (sepsis, shock, non-lung traumas)\(^6\). The distinction between primary and acquired (while in ICU) diagnoses, however, becomes somewhat ambiguous in MODS. Though effective treatment of the underlying problem can be required for successful achievement of stable hemodynamics and renal, hepatic, and pulmonary function. A concrete illustration can help explain this point. Consider the following case study from Seiver in *The High Risk Patient: Management of the Critically Ill*.

"For example, gastrointestinal failure secondary to hypoperfusion and inadequate nutrition [ICU issues that may or may not be related to primary diagnosis] is associated with an ileus that enables bacterial overgrowth in the normally sterile stomach and small bowel. These bacteria- particularly the virulent organisms selected by antibiotics- may migrate up the intestinal lumen or through the intestinal wall (bacterial translocation). Migration into the upper gastrointestinal tract can colonize the pharynx and then the trachea leading to nosocomial pneumonias. Translocation may lead to seeding of the peritoneal cavity and the portal circulation. The hepatic macrophages

\(^6\) ibid.
(Kupffer's cells) may not be able to clear the portal circulation, and systemic bacteremia may occur.7"

So in this case hepatic or pulmonary dysfunction may arise from metabolic, hemodynamic, and other post-surgical complications in the context of the primary injury. There may have been a GI resection potentiating hemorrhage and resultant hypoperfusion or there may have been a global hypoperfusion/hypermetabolism forcing the patient into a relative oxygen debt.

Whatever the case may be, it is pulmonary dysfunction which is most characteristic of the onset of MODS, and it is Adult Respiratory Distress Syndrome which is the most characteristic heralding manifestation of pulmonary pathology8. From Schwartz et. al. we have...

"The fundamental lesion of ARDS is an increase in microvascular permeability which permits egress of water and large molecular weight


solute from the intravascular compartment into the pulmonary interstitium and eventually into the alveoli, resulting in pulmonary edema.⁹"

To this Barton/Cerra add ARDS is..."characterized by endothelial cell injury and destruction, deposition of platelet and WBC aggregates in clots of fibrin and cellular debris, destruction of type 1 alveolar pneumocytes, and an acute inflammatory response that must proceed through all phases of repair, a process not unlike active wound healing in other parts of the body. These alterations become manifest clinically as decreased lung compliance, mismatching of ventilation and perfusion, arterial hypoxemia...¹⁰"

It is interesting to note that while ARDS usually precedes hepatic and renal failure in MODS, Schwartz et. al. concluded in their study of ARDS patients that "Although there were no significant differences in the indices of pulmonary or renal dysfunction between survivors and non survivors, evidence of hepatic dysfunction was different in the two groups.¹¹"

---


Hepatic dysfunction therefore appears to be central to development of MODS whereas ARDS may occur with or without MODS. Schwartz et. al. note that endothelial injury such as that described for pulmonary endothelial cells above is also seen in the liver. And though lab evidence of liver failure usually lags evidence of decline in pulmonary function, the liver's pivotal role in the body's defenses make's its injury a reinforcing step in the syndrome's progression against other organs.

"Microvascular injury characteristic of ARDS may not be restricted to the pulmonary vasculature. Hepatic microvascular permeability also may be increased. Morphometric studies of a canine poly traumatic shock model showed swollen Kupffer cells, sinusoidal endothelial swelling and widening of Disse's spaces. As described in the lung...hepatic dysfunction might result from vascular damage, edema, or both.

Intrahepatic edema may interfere with the reticuloendothelial system host defenses, in a fashion similar to pulmonary edema, as decreased sinusoidal flow has been associated with severe depression in phagocytic activity. The liver has a significant role in host defense mechanisms....Intact hepatic function may be important in preserving the systemic response to infection.

Additionally, the liver may protect the lung; the reticuloendothelial system removes circulating substances which may potentiate acute lung injury and hepatocellular processes may metabolize potential mediators of acute lung
injury. Finally, hepatic edema may contribute to or complicate inadequate cellular oxygenation resulting in hepatocellular damage of dysfunction that is thought to be pivotal in the development of multiple systems organ failure.\textsuperscript{12}\textsuperscript{12}

The endothelial injury in these organs can certainly be caused by sepsis, and much has been written about that as well as the role of endotoxins. The case study provided above illustrated translocation of microorganisms and an ensuing bacteremia. It is important to stress, however, that while the importance of endotoxin should not be underestimated, "it almost certainly requires other mediators to elicit its effects.\textsuperscript{13}\textsuperscript{13}" Many cases of MODS do not develop in the context of sepsis and septic complications, as indicated in the passage above, can follow liver dysfunction.

This points to a pathophysiology of 'inflammatory response.' A person with a severe leg injury and no initial pelvic, abdominal, or chest injury, on antibiotics with no apparent bacteremia can four or five days later begin to show pulmonary and hepatic insults as well as sepsis. Sepsis may feed into the pathophysiologic process in question, but the underlying process appears to be a maladaptive over-reaction of the bodies fundamental

\textsuperscript{12} ibid, p. 874

\textsuperscript{13} Barton, Cerra, The Hypermetabolism Multiple Organ Failure Syndrome, Chest, November 1989, 96(5):1157.
inflammatory responses which can develop independently from and may actually cause sepsis or expand a local insult.

The hypothesis is not dissimilar from the concepts employed in Seiver's description of translocation above. In that case, microorganisms are seeded which elicit inflammatory mediators causing cell damage. However, at the heart of the MODS phenomenon appears to be the idea that the mediators themselves can be seeded, either independently from or concurrently with microorganisms, resulting in the same damage that can lead to organ dysfunction.

Barton and Cerra note that "mechanistically, the hypermetabolism/MODS is best thought of as a systemic extension of the local inflammatory response. The initial events appear to occur in the microcirculation. The initiating event is usually associated with a reduction in microcirculatory perfusion that induces endothelial cell injury, platelet aggregation, infiltration of neutrophils, and activation of the complement kallikrein-kinin, coagulation and fibrinolysis cascades, as well as cytokine release."¹⁴

Note that at this point, the endothelium involved need not be of an internal organ. It could be any trauma such as on the leg of a motorcyclist who had

---

¹⁴ ibid.
an accident or a roofer who broke an arm in a fall. No bacteremia may have occurred and the patient may be responding well to antibiotics.

Barton and Cerra continue..."Increased capillary permeability leads to further losses of intravascular volume into the extravascular space, aggravating the existing perfusion deficit. With reperfusion, cell debris and a variety of toxic inflammatory mediators are released into the systemic circulation, contributing to continued injury locally and at distant sites such as lung and liver.

It seems reasonable to hypothesize that the shock and reperfusion phases have the microcirculation and the endothelial cell as their targets. The neuroendocrine axis, platelets, and the PMN (neutrophil) appear to be the primary effectors in these early stages. After resuscitation, the phase of stable hypermetabolism is entered...Even when sepsis is no the initiating event, it is virtually always a problem as the syndrome progresses, whether as the result or the cause of the organ failure process.¹⁵"

"This has been termed", Seiver notes, "the systemic inflammatory response syndrome...If the process cannot be contained, ...inflammatory mediators are dispersed and begin to circulate systemically, thereby activating numerous humoral factors. The collection of circulating activated factors,

¹⁵ ibid.
including oxygen radicals, proteases, aggregated platelets, prostaglandins, leukotrienes, and cytokines, causes endothelial damage and microvascular thrombosis. Ultimately this damage and thrombosis leads to tissue injury and destruction, which manifests as organ dysfunction and organ system failure.

Each vital organ of the body has its own finite ability to sustain function in the face of, or recuperate from, significant microvascular injury. The delicate pulmonary tissues are the most sensitive to these critical changes, and intrapulmonary damage is the first to manifest with the onset of sepsis...It is important to note that SIRS may be seen following a significant degree of tissue injury (i.e. in trauma, pancreatitis, and large burns), and therefore the severe clinical course associated with this entity is not exclusively linked to underlying infection...

In addition to organ dysfunction and failure, SIRS is associated with a marked increase in metabolic demand...this hypermetabolism may be prolonged and can persist for weeks in the critically ill patient. During this time, there is marked increase in energy expenditure, oxygen consumption and carbon dioxide production.\textsuperscript{16} This is characterized by an increased metabolic rate that may exceed twice the basal metabolic rate.\textsuperscript{17}

\hspace{1cm}

The subject of this study, an oxygen deficit, develops when demand outstrips supply. The demands of hypermetabolism, coupled with the insult to delivering from "endothelial injury, microvascular thrombosis, and other microvascular changes seen with the inflammatory response are associated with impaired vasoregulation and an inability to match perfusion to metabolic needs.\textsuperscript{18}

Hemorrhage, and the increased permeability of the endothelium due to injury and circulating activated factors sequester volume in the interstitium (extracellular space), which reduces the preload to the heart and created hemodynamic instability. These factors limit peripheral perfusion, as does the thrombosis. This is significant because at the same time peripheral demand rises due to the cell injury discussed above superimposed on the need for healing wounds and fighting infections.

---

Williams & Wilkins, 1995.

\textsuperscript{17} Barton, Cerra, \textit{The Hypermetabolism Multiple Organ Failure Syndrome}, \textit{Chest}, November 1989, 96(5):1155.

In the context of an increased peripheral demand, the cardiac output needs to increase. If the preload is low due to an increase in permeability of microcirculation, cardiac output must be increased by an increase in sympathetic stimulation and heart rate, often supported by inotropic intravenous medication. In elderly patients, the heart may be weakened and unable to sustain the metabolic needs imposed. Sympathetic clamping further reduces peripheral perfusion.

Compounding the endothelial damage, thrombosis, and sympathetic clamping in this syndrome is a dropping albumin level as liver function falters. This reduces osmotic pressure in the vessels, further supporting the effusion of fluid to the interstitial space, and thus further lowering preload. In the hypermetabolic environment, this puts more pressure on heavy sympathetic stimulation exacerbating the poor peripheral perfusion...a viscous cycle.

"Resuscitation of the microcirculation is the most important therapeutic intervention," Barton and Cerra comment. "Unfortunately, hemodynamic restoration and urine output are often inadequate; and persistent, subclinical circulatory shock remains one of the primary causes of hypermetabolism (due to cell injury) and organ failure."^{10}

---

Perfusion limitations from thrombosis, endothelial injury, microvascular changes, hemorrhages, and albumin deficiencies all detract from tissue oxygen delivery. Seiver comments..."the patient's oxygen extraction curve thus demonstrates a diminished slope in the face of an increased plateau of need...this results in supply dependent oxygen consumption...In the face of an increasing oxygen debt, a recurring cycle of ischemic damage, increased oxygen demand, failure to fulfill the demand, and continuing damage occurs. Although this entire cascade may begin in response to a...locus, it can swiftly develop into far-reaching systemic effects...the inflammatory response is sustained or even heightened by secondary infection, creating an even greater oxygen debt...thus, inflammatory response can become increasingly severe with magnified deleterious effects. The phrase 'inflammatory anarchy' has been used to describe these events...Initial humoral activation leads to endothelial injury, hypermetabolism, and tissue nutrient deprivation, each of which contributes to organ dysfunction, secondary infection, and a continued humoral activation with a recurring cycle of insult and injury. Ultimately, this cycle of ongoing tissue injury, organ dysfunction, and organ failure leads to a patient's demise.20"

This leads us to the underpinnings of the design for this clinical study. As Barton and Cerra put it: "ideally, the end point of adequate microcirculatory resuscitation is attainment of flow-independent oxygen consumption and lactate production, meaning that oxygen delivery (DO2) is increased until oxygen consumption (VO2) no longer rises and lactate production no longer falls." This means that in response to supply dependent oxygen consumption, markedly increased oxygen delivery is necessary until the oxygen consumption is flow-independent.

The chart below is a rough copy of a chart Seiver uses to explain the concept.

---

Hypermetabolic patients "have a capacity to extract oxygen that is lower than that of normal patients. The oxygen demand, however, is higher...The rate at which the oxygen debt develops is the difference between the oxygen consumption and the oxygen demand...[hypermetabolic] patients may accumulate oxygen debt even at normal delivery because the rate of extraction is lower and the demand is higher. The normal patient would exhibit an equivalent debt rate only at much lower than normal oxygen..."
delivery. This provides a rational for supranormal values for oxygen delivery as a therapeutic goal...\textsuperscript{22}

The question which then arises is how one knows when the therapeutic goal has been achieved. Traditional clinical measures for shock are lactic acidosis, oliguria or anuria, and cyanosis. The idea of this study was to test a technique that would function as an earlier predictor or indicator.

The main problem with finding a quantitative endpoint for resuscitation is that what would be enough in a typical patient is not enough in a hypermetabolic patient Swan-Ganz catheters placed through the heart into the pulmonary artery such as are used in this study are often an important part of monitoring\textsuperscript{23}. Monitoring of hemodynamic parameters are (e.g. cardiac output) crucial. Interestingly, another justification for use of this invasive catheter is to monitor the pulmonary artery pressures. In a situation where is never clear when the patient is fully resuscitated, one quantitative endpoint is that point at which resuscitation has pushed pulmonary artery pressures so high as to itself cause more pulmonary edema. This is counterproductive as it impairs gas exchange in the lung and


\textsuperscript{23}
causes arterial hypoxemia. This, and not wanting to place unnecessary stresses on the heart are both good reasons to be able to reduce resuscitation once flow-independent oxygen consumption is reached.

According to the Seiver graphic and the Barton/Cerra description, full resuscitation occurs where an incremental increase in O2 delivery causes no increase in O2 consumption. This is the basis for the study design here.
II. METHODOLOGY

II. 1. Overview of Study Design

This study is an observational explanatory study since it seeks primary to identify a predictor for better diagnosis. It is structures as a follow-up or cohort study since measures are taken before the outcome is known.

Patient were selected from the trauma and surgical services from the SICU. The only other inclusion criteria was that a Swan-Ganz catheter must be placed for the patient to be enrolled as a study subject. Prospective enrollees typically could not be conferred with since they were sedated and unconscious. Family members were approached and the Consent Form was explained to them. Patient's families were provided with the study coordinator's pager number at the hospital and were also made aware that if, at any time, for any reason, they wished to back out, they could. Although it is stated above, it is worth re-emphasizing that all family members of prospective enrollees were made aware that deciding not to do the study would in no way affect the quality of care. In cases where a family's primary language was not English, a translator was provided.

Patient's who were initially enrolled were dis-enrolled if, at the time of the peripheral catheter placement, difficulty was encountered in the stable placement of the line. For example, if numerous sticks were necessary to
find an appropriate peripheral vein, the endeavor was abandoned and the patient was not enrolled in the study. This occurred several times with woman whose veins were very small. It also occurred in several patients who were so edematous that a vein became to difficult to find to justify continuing.
II. ii. The Measure

The measure in this study is what happens to oxygen consumption when oxygen delivery is incrementally increased. FiO2 on the patient's ventilator is turned up to 100% for five minutes. The patient's blood is sampled both before and after from three different lines; arterial (usually radial), central venous (from the Swan-Ganz catheter), and peripheral venous (from a peripheral venous catheter).

The basis for measuring oxygen debt with the concept described below is to create a rapid change and measure the physiologic response to that change. Some common changes or perturbations are oxygen flux tests using dobutamine and cardiac stress tests using a treadmill. Creating a rapid perturbation and measuring the physiologic response provides a much faster and accurate method of determining imbalances in oxygenation than simply trending changes over long periods of time. Another means of creating a fast perturbation is to rapidly increase oxygen to the patient by increasing FiO2. Increasing oxygen is transparent to most of the body. Excess oxygen passes through the venous organs and into the venous circulatory system. Flux tests using drugs, such as dobutamine, significantly alter the hemodynamic status of the patient making interpretation of results difficult at best. Short exposures to increased oxygen, unlike elevated CO2 and dobutamine, has little effect of the patient's hemodynamic status. Various techniques, invasive and non-invasive, measure circulating oxygen in the
bloodstream. The volume of oxygen in the arterial or venous bloodstream is quantified using the oxygen content equations, where:

\[ \text{CXO}_2 = 1.34 \times \text{SXO}_2 \times \text{THb} + 0.0031 \times \text{PxO}_2 \]

(x denotes either arterial or venous)

Delivering concentrated oxygen to the patient is an efficient means of increasing the oxygen content of blood. Since normal arterial oxygen saturation is close to 100%, additional oxygen circulates to the organ of interest as dissolved oxygen in plasma. By breathing pure oxygen for about 5 minutes, oxygen tension of whole blood increases to about 300-500 mmHg, given normal pulmonary function. This represents a 5-10% increase in oxygen delivery without changing flow or other characteristics of whole blood. Increasing oxygen for short periods of time also has little effect of the patient's hemodynamic status.

Using CXO2 to quantify changes in oxygen delivery, one can measure the oxygen inflow to and outflow from an organ simultaneously. By creating an oxygen perturbation, the inflow and outflow oxygen saturation is measured over very short periods of time. Using this method, regional organ measurements can easily be made. Assuming blood flow to be constant over short periods of time (5 minutes), the regional oxygen content into and out of the organ of interest can be measured.
Oxygen utilization is the difference between the arterial oxygen content (CaO2) and the venous content (CVO2) and relates to oxygen consumption through cardiac output. In the flow independent consumption state, organs have sufficient oxygen to meet all metabolic needs. Supplemental oxygen does not produce increases in extraction or oxygen utilization. In the flow dependent consumption state, oxygen utilization is dependent on delivery. When oxygen delivery increases, the organ consumes more oxygen until all metabolic needs are met.

In fully resuscitated patients, oxygen consumption is independent of oxygen delivery. Increasing oxygen delivery does not result in increases in oxygen consumption. Therefore, as oxygen delivery increases by increasing oxygen content, via an oxygen challenge, oxygen consumption remains constant. The change in the quantity of oxygen into and out of the organ is equal, or described by \( \Delta \text{O}_2\text{in} = \Delta \text{O}_2\text{out} \). In under resuscitated patients where flow dependent consumption occurs, changes in oxygen into the organ is greater than the change from the organ, indicating an increase in consumption, or \( \Delta \text{O}_2\text{in} > \Delta \text{O}_2\text{out} \). Oxygen debt of an organ is defined as \( \text{O}_2\text{ debt} = \Delta \text{O}_2\text{out} - \Delta \text{O}_2\text{in} \).

One calculates oxygen debt using the oxygen content equations. To measure the quantity of oxygen into and out of the organ use the relationship:
CX02 = 1.34 x SX02 x THb + 0.0031 x Px02

(x denotes either arterial or venous)

The change in the quantity of oxygen due to the oxygen challenge becomes
\[\Delta CX02 = 1.34 \times \Delta SX02 \times THb + 0.0031 \times \Delta Px02\]

Oxygen debt is calculated from the following relationships:

\[02 \text{ debt} = \Delta O2\text{out} - \Delta O2\text{in}\]

\[02 \text{ debt} = \Delta C2v - \Delta O2a\]

\[02 \text{ debt} = \Delta CvO2 - \Delta CaO2\]

\[02 \text{ debt} = 1.34 \times (\Delta SvO2 - SaO2) \times THb + 0.0031 \times (\Delta PvO2 - \Delta PaO2)\]
II. iii. The Clinical Course/Outcome

Non-survival is one important outcome assessed in the study. Because it helps elucidate the clinical course of the patient during the ICU stay and because it helps elucidate the pathophysiology, organ scoring was also employed. Organ scored here are therefore additional proxies for clinical course.

There are several different models that have been developed and they have different applications. Therefore, it is necessary to justify why the MODS model was employed, and describe its credibility basis and something about how it has been developed and tested. The main point of this is that MODS is a proxy that is already proven to be correlated to clinical outcome. Therefore, comparing the prognostic ability of the study measure to that of the MODS is useful to do in addition to comparing the measure to whether the subjects lived or died.

Marshall saw assessment of organ function as both "a reflection of the severity of physiologic derangement over time ... of the degree of therapeutic intervention required...and so that prophylactic or therapeutic interventions can be evaluated."\(^{24}\)

\(^{24}\) ibid p, 39.
It is noteworthy that organ rating per se, and not primary diagnosis, has been utilized by researchers. For example, Le Gall and Lemeshow's SAPS II and MPM II Models for Early Severe Sepsis, the authors frame this concept in their description of the sepsis syndrome as a set of "clinical and biology manifestations." Evidence of hypotension, systemic inflammatory response, or multiple organ failure were stressed over presenting diagnosis.

Factors related to presenting diagnosis (for instance, cirrhosis) were numerous. Le Gall and Lemeshow tested many of them and concluded that while they "provide accurate estimates of the probability of mortality...on the other hand the customization [i.e. organ descriptors] technique resulted in high-performance models without them having to be made more complicated." (1: p. 161) This was held in a subsequent publication to be a major improvement on APACHE, APACHE II, and SAPS.

In A New Simplified Acute Physiology Score (SAPS II) Based on a European/North American Multicenter Study, Le Gall, Lemeshow, and

---


26 ibid p. 158.

27 ibid p. 161.
Saulnier note their preference for "an estimate of the risk of death" independent of a primary diagnosis.\textsuperscript{28} "While some patients can be categorized according to a specific, simple, and unique diagnosis," the researchers explain, "such as chronic obstructive pulmonary disease, septic shock, or barbiturate overdose, this is not the case in general. In fact, for the patients in that study, it was possible to categorize only 37\% of patients into only one diagnostic category, with remaining patients having multiple diagnoses...When ICU patients do have several diagnoses, it is often problematic to select the most important one. For example, if a patient has adult respiratory distress syndrome and associated pulmonary peritonitis, which is the main diagnosis?\textsuperscript{29}"

In his study, \textit{A Scoring System for Multiple Organ Dysfunction Syndrome}, J. C. Marshall adds..."critically ill patients admitted to a contemporary intensive care unit rarely die as a consequence of the progression of the disease process which resulted in their admission to hospital.\textsuperscript{30}" "Instead,"

\begin{flushright}
\textsuperscript{28} Le Gall JR, Lemeshow S, Saulnier F: \textit{A new simplified acute physiology score (SAPS II) based on a European/North American multicenter study}. \textit{JAMA} 270:2957, 1993.

\textsuperscript{29} ibid p. 2960.

\end{flushright}
Marshall notes, "the most common cause of mortality in the ICU is a syndrome variously known as multiple system failure, multiple organ failure...or, more recently, multiple organ dysfunction syndrome (MODS).\textsuperscript{31}" Evaluating the progression of a patient's clinical status after arriving in the ICU is critical according to Marshall, who defines MODS as "a clinical syndrome characterized by the development of progressive...physiologic dysfunction developing in two or more organs or organ systems."\textsuperscript{32}

Marshall's emphasis on dynamic organ status has brought to issue an important distinction between the MODS and SAPS II/MPM/APACHE II approach by way of a classification that has developed between...

* primary MODS, rising "immediately after" and "as a direct consequence of"..."the process responsible for that insult," (e.g. coagulopathy following massive blood loss and transfusion); and,

* secondary MODS, which "develops later and arises as a result of the host response to the primary disease process" (e.g. ARDS in response to peritonitis).\textsuperscript{33}

\textsuperscript{31} ibid.
\textsuperscript{32} ibid.
\textsuperscript{33} ibid.
"Arising in the wake of an acute threat to homeostasis," Marshall explains, "the syndrome can be initiated by...infection, ischemia, injury, and inflammation" which are "at least partially...amenable to therapeutic manipulation." Marshall's concept of MODS as a set of biological manifestations suggested to him that a model ideally ought to be designed and tested to maintain its integrity over the continuity of the patients ICU stay, both to aid in the understanding the pathophysiologic processes linked to the evolution of MODS, as well as to have a control with which to evaluate diagnostic criteria and the amenability of manifestations of the syndrome therapeutic interventions.

This aspect of MODS led to its application as a prognostic indicator and outcome measure when assessed as a series and calculated over the course of an ICU stay. It has also been suggested because serial MODS as an outcome measure could substitute for mortality as an endpoint in clinical trials, "more subtle biologic changes can be detected using smaller groups of patients than are required for mortality studies" and that MODS

34 ibid.


stratified by admission APACHE II is could be considered as "a measure of the quality of care provided in a particular ICU.\textsuperscript{37}"

This was not the case for SAPS II/MPM/APACHE II which were designed specifically for assessing very early and severe sepsis. In the refined SAPS II and MPM II24, data was collected only for the first 24 hours of the ICU stay so the proposed models are "only for...the first ICU day...the first 24 hours.\textsuperscript{38}" A result of this is that when, for the original SAPS II model, a "28-day survival curve were construed to examine the differential survival between severe sepsis patients and all others...SAPS II and MPM II24 did not fit the data well.\textsuperscript{39}" and the authors had to fit with multiple regression techniques.

Le Gall, Lemeshow, and Saulnier conclude that the SAPSII does is not an efficient way to evaluate the progression of the risk of death after the first 24 hours\textsuperscript{40}. In a separate publication, Le Gall and Lemeshaw indicate that

\textsuperscript{37} ibid.


\textsuperscript{39} ibid p. 159.

\textsuperscript{40} Le Gall JR, Lemeshow S, Saulnier F: \textit{A new simplified acute physiology score} (SAPS II) based on a European/North American multicenter study. \textit{JAMA} 270:2962,
although it would be desirable to develop models for use among patients after the 24th hour\textsuperscript{41}, this cannot simply be addressed by using a newly computed score according. Rather, it would require a new process of re-customizing and re-fitting the model with new multiple regression data to reflect the changing mortality patterns at two days, at three days, at four days, etc...\textsuperscript{42}. This is not available and therefore would make the use of SAPS II and MPMII24 other than for early and severe sepsis (i.e. after the first 24 hours) comparable to the researchers experience prior to the original logistic fitting (where, as stated above, "SAPS II and MPM II24 did not fit the data well\textsuperscript{43}").

One of the interesting contrasts that a model designed for continuous monitoring raises relates to the 'worst-score' approach. In the SAPS II based on the European/North American Multicenter study, "the physiological variables were recorded by the data collectors as the worst value in the first 24-hour period in the ICU.\textsuperscript{44}" For MODS, Marshall

\begin{footnotesize}
\begin{itemize}
\item[\textsuperscript{42}] ibid.
\item[\textsuperscript{43}] ibid p. 159.
\item[\textsuperscript{44}] Le Gall JR, Lemeshow S, Saulnier F: \textit{A new simplified acute physiology score}
\end{itemize}
\end{footnotesize}
notes..."within each system, abnormal values are those present at a standard time of assessment...rather than the worst values over 24 hours to minimize the impact of marked, but transient, functional abnormalities as might occur, for example, as a consequence of a mucus plug in the airway. In turn, MODS then calculates the score by "summing the worst scores for each of the individual systems over the ICU stay.""

In our case, a predictive proxy for mortality is useful and a concrete example of the advantage of the MODS approach for our needs is illustrated in the research. Both on the first day and over the course of the ICU stay, MODS showed excellent discrimination. "ICU mortality was approx. 25% at 9-12 points, 50% at 13-16 points, 75% at 17-20 points, and 100% at levels of >20 points." By contrast, "reports of mortality rates...differ


47 ibid p. 1641.

48 ibid p. 1638.
widely...in the European-North American database" where "the repartition of risk of death varies in the group...from 0.01 to 0.99.  

Another factor favoring MODS for our study is the fact that MODS was designed specifically "to use ICU mortality, rather than hospital mortality, as the endpoint to evaluate candidate variables, since intrinsic to the concept of MODS is the need for ICU support and the consequences of its success or failure." Data was collected from 692 admissions to the surgical intensive care unit of Victoria General Hospital in Halifax, Nova Scotia, Canada. The SAPS II was built from a European/North American study involving patients from "medical, surgical, and mixed ICUs" in 10 European and two North American countries.


51 ibid, pp. 43-44.

Finally, a brief description of the MODS descriptors and a sample of a grid are in order. Marshall points out that "there is as yet no consensus on the criteria necessary to define the syndrome," and that therefore we are confronted with "an ongoing project to refine and validate diagnostic criteria for the organ systems in question."

A review of 19 published reports on multiple organ dysfunction system, seven organ system appear in more than half of the reports: respiratory, renal, hepatic, cardiovascular, hematologic, central nervous, and gastrointestinal. A second computerized database review, performed in 1995, of MEDLINE clinical studies of multiple organ failure published between 1969 and 1993 identified the same seven systems again in more than half of the 30 studies identified.

- Although mentioned in 13 of 19 in the first study and 22 of 30 of the second, GI dysfunction was omitted in the scoring system due to difficulties


54 ibid.

55 ibid p. 40.

in developing a 'reliable continuous descriptor' because stress bleeding has become less common, diarrhea and enteral feed intolerance are difficult to quantitate, and nasogastric drainage showed no correlation with ICU mortality⁵⁷.

• The Glasgow score was used as the proxy for neurologic dysfunction. Although its evaluation does involve clinical evaluation, sedation affects it, and it may be a reflection of primary disease in the head-injured patient, three factors supported its use⁵⁸. First, Glasgow Coma Scores were significantly lower in nonsurvivors than survivors and worked better than presence of meningitis or hemorrhage. Second, conservative estimates can address the sedation problem (i.e. estimates of what the Glasgow would be if the patient were not sedated). Third, it was still less subjective than other criteria authors used such as confusion, obtundation, or psychosis.

• All 19 studies in the first review and all 30 studies in the second review identified respiratory dysfunction as a manifestation of MODS, using variables "reflecting the need for, duration of, and/or mode of mechanical ventilation."⁵⁹ Abnormality of PO2/FiO2 ratio (lower) and PEEP (higher) were both found non survivors relative to survivors (PCO2 did not

⁵⁷ ibid, p. 1645.
⁵⁸ ibid.
⁵⁹ ibid p. 1642.
correlate). PO2/FiO2 was chosen, and its main shortcoming (manipulation by change in PEEP or ventilation rate) did not affect the graded correlation. Mortality was 0% when this ratio was always >300 and 50% when the worst value was <75\textsuperscript{60}.

- Cardiovascular proxies were numerous, including hypotension, pressors, dysrhythmias, MI, tamponade, and endocarditis. The only one which demonstrated mortality >50% at the highest level of dysfunction was blood pressure\textsuperscript{61}. However, a graded correlation (i.e. intervals of increasing abnormality) were not present, due to susceptibility of the measure to changes from resuscitation and therapy. A composite measure (HR * CVP/MAP) was therefore developed to correct for physiologic support\textsuperscript{62}.

- Renal dysfunction was included in all 19 of the studies in the first review and all but one of the 30 studies in the second. Although, some described oliguria, need for dialysis, acid-base or electrolyte homeostasis, it was most commonly defined as serum creatinine, which was significantly higher for non survivors\textsuperscript{63}. Serum creatinine 'independent' of preexisting chronic

\textsuperscript{60} ibid.

\textsuperscript{61} ibid p. 1644.

\textsuperscript{62} ibid.

\textsuperscript{63} ibid p. 1643.
renal failure was used. Qualification also must be made in dialysis where concentration can be lowered independent of intrinsic renal function).

- 18 of 19 studies cited hepatic dysfunction in the first review and 27 of 30 in the second. Measures included serum bilirubin, serum albumin, transaminases, Alk Phos, and LDH. Differences were evident between survivors and non survivors in all these categories. No single variable predicted mortality of >50% at the highest increment of abnormality\(^{64}\). In spite of the potential for hemolysis to impact readings and limited ability to reflect the full range of hepatic illness, serum bilirubin as chosen for "construct validity and simplicity" as it satisfied most the criteria for a good descriptor\(^{65}\).

- Thrombocytopenia was the most common manifestation cited for hematologic abnormality and platelet counts were lower for non survivors with graded correlation.

\(^{64}\) ibid.

\(^{65}\) ibid.
III. Data Analysis/Discussion/Conclusions

The 'Measure' in this experiment is the O2 Deficit. The 'Outcome' is assessed both by the MOD score as well as by the Clinical Path of the patient in the ICU.

In regard to the Measure, there are two O2 Deficits numbers that are constructed: the Peripheral Blood O2 Debt using the peripheral venous blood and the Central O2 Debt using pulmonary artery blood from the Swan-Ganz catheter. This approach is supposed to serve as a predictor. Ideally, O2 Debt would be sensed before systemic signs of shock such as lactic acidosis and organ dysfunction. If a Central O2 Debt were to occur, there would clearly already be a lactic acidosis and the central organs whose blood flow is returning to the pulmonary artery would presumably already be in debt and suffering cellular injury.

If the body were to try to protect the internal organs, it follows that the peripheral vascular beds would be clamped down first as a means to divert blood flow to the internal organs if a situation of energy rationing arose. Therefore, the signal that was looked for is a rise in Peripheral O2 debt before a rise in Central O2 debt. The pathophysiologic sequence expected if this technique worked would be a Peripheral O2 debt that was growing and large relative to the Central O2 debt, followed by a worsening MOD score, followed by a protracted and critical ICU stay and perhaps death.
The O2 calculation discussed above is constructed so that O2 Debt is a positive number and good resuscitation appears as a negative number. Once calculated, the Peripheral and Central O2 Debts were plotted against time for each of the 18 study subjects. To familiarize yourself with the plots in order to appreciate the summary tables, you may view these plots at your leisure beginning on page 45. They appear after the summary discussion here. In short, the signal being assessed consists of the Peripheral O2 line rising very close to or crossing the Central O2 line, thus indicating the normal situation of Peripheral O2 surplus in the arm relative to the pulmonary artery has been changed by the body clamping down on the peripheral circulation.

If this technique worked, one would expect cases where the Peripheral O2 line came close to the Central O2 line (significantly 'closing the gap') or where the Peripheral O2 line actually crossed the Central O2 line to be found in subjects who would go on to have the higher MOD scores and greater morbidity and mortality in their ICU stays.

In regard to the MOD score, the research discussed in some detail above concluded..."ICU mortality was approx. 25% at 9-12 points, 50% at 13-16 points, 75% at 17-20 points, and 100% at levels of >20 points. High MOD score is a proxy for the development of multiple organ dysfunction.

ibid p. 1638.
In regard, to clinical outcome, three categories are defined; 1) death, 2) very critical multiple organ failure and protracted course but ultimately survived, 3) improved and transferred out of ICU without serious multiple organ failure. Any subject who were in groups 1 or group 2 (death or protracted multiple organ failure), would be expected to have a Peripheral O2 debt signal (as indicated by nearing or crossing the Central O2 line) if this technique worked. Below is a summary table of the findings.
<table>
<thead>
<tr>
<th>Case</th>
<th>Clinical Outcome</th>
<th>MOD Score</th>
<th>Did MOD &gt; 9 correlate with poor outcome?</th>
<th>Did Peripheral O2 Debt near Systemic Debt?</th>
<th>DID SIGNAL WORK?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1-death</td>
<td>12</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>2</td>
<td>3-improved</td>
<td>2</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>3</td>
<td>1-death</td>
<td>13</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>4</td>
<td>1-death</td>
<td>8</td>
<td>FALSE NEG.</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>5</td>
<td>2-serious</td>
<td>7</td>
<td>FALSE NEG.</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>6</td>
<td>3-improved</td>
<td>9</td>
<td>FALSE POS.</td>
<td>YES</td>
<td>FALSE POS.</td>
</tr>
<tr>
<td>7</td>
<td>2-serious</td>
<td>11</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>8</td>
<td>3-improved</td>
<td>5</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>9</td>
<td>1-death</td>
<td>13</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>10</td>
<td>1-death</td>
<td>14</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>11</td>
<td>3-improved</td>
<td>8</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>12</td>
<td>1-death</td>
<td>16</td>
<td>YES</td>
<td>YES</td>
<td>YES</td>
</tr>
<tr>
<td>13</td>
<td>3-improved</td>
<td>7</td>
<td>YES</td>
<td>YES</td>
<td>FALSE POS.</td>
</tr>
<tr>
<td>14</td>
<td>3-improved</td>
<td>3</td>
<td>YES</td>
<td>YES</td>
<td>FALSE POS.</td>
</tr>
<tr>
<td>15</td>
<td>3-improved</td>
<td>6</td>
<td>YES</td>
<td>YES</td>
<td>FALSE POS.</td>
</tr>
<tr>
<td>16</td>
<td>3-improved</td>
<td>5</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
<tr>
<td>17</td>
<td>3-improved</td>
<td>10</td>
<td>FALSE POS.</td>
<td>YES</td>
<td>FALSE POS.</td>
</tr>
<tr>
<td>18</td>
<td>3-improved</td>
<td>6</td>
<td>YES</td>
<td>NO</td>
<td>YES</td>
</tr>
</tbody>
</table>
This method worked as an early signal provided the desired result in 13 of 18 cases. Further, the method detected every subject who subsequently encountered severe morbidity or mortality in the ICU. All five mistakes were false positives. Notably, the MOD score was 14 of 18, however with 2 false positives and missing one death and one serious morbidity.

The conclusion is that the technique is promising. It was decided after 18 subjects that due to the highly invasive approach we utilized, it would be better to discontinue further measurements until Baxter had developed a dual-mode non-invasive oximeter that would accurately measure venous as well as arterial O2 saturation. The technology of stabilizing the venous measurement is not currently available.

Experimental Error: The size of the 4-French peripheral venous catheter required it be placed at the cubital fossa or higher. Lines placed below the cubital fossa blew out quickly and ceased to draw due to the small size of the veins there. As a result the end of the catheter would extend well into the upper arm. Particularly in smaller subjects, this introduced the possibility of some back draw from the subclavian. The subclavian receives scapular, pectoral, and head and neck venous blood which would impair the purity of the draw as a strict measure of peripheral venous blood. In most cases, there were probably patent valves sealing the back leak from the subclavian. But it is also possible that some patients had imatencies which allowed some backdraw. Vessels from the head, neck, scapular, or pectoral
regions would theoretically not be clamped as soon as extremity vessels in shock, and so could dampen the signal quality of the technique.
8:00 pm 4/14/96  MODS SCORE = 12
PO2 = 117
FiO2 = 0.45
Serum Creatinine = 371.994 umol/L
Serum Bilirubin = 93.775 umol/L
HR = 115
CVP = 13
MAP = 83
Platelet Count = 38

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td></td>
<td>260</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td></td>
<td></td>
<td>371.994</td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td>93.775</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td>18.012</td>
<td>24.44*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>=</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
3:30 am 5/23/96  MODS SCORE = 2
PO₂ = 95
FiO₂ = 0.4
Serum Creatinine = 70.856 umol/L
Serum Bilirubin = 10.23 umol/L
HR = 83
CVP = 6
MAP = 93
Platelet Count = 288

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO₂ / FiO₂)</td>
<td></td>
<td></td>
<td>235.7</td>
<td>202.5*</td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td>70.856</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td>10.23</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR x CVP / MAP)</td>
<td>5.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td>288</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
Organ System | 0   | 1    | 2    | 3    | 4    |
-------------|-----|------|------|------|------|
Respiratory  |     | 271.42 |     |      |      |
(PO2 / FiO2) |     |       |      |      |      |
Renal        |     |      |      | 389.70 |      |
(Serum Creatinine) |     |      |      |      |      |
Hepatic      |     |      |      | 306.9 |      |
(Serum Bilirubin) |     |      |      |      |      |
Cardiovascular|     | 5.38 |      | 15.54* |      |
(HR X CVP / MAP) |     |      |      |      |      |
Hematologic  |     |      |      | 28   |      |
(Platelet Count) |     |      |      |      |      |
Neurologic   |     |      |      |      |      |
(glasgow)    |     |      |      |      |      |
TOTAL SCORE  | -13 |      |      |      |      |

* Denotes previous worst organ score.
3:35 am 5/27/96 MODS SCORE = 8
PO2 = 93
FiO2 = 0.4
Serum Creatinine = 97.427 umol/L
Serum Bilirubin = 32.395 umol/L
HR = 122
CVP = 11
MAP = 56
Platelet Count = 103

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td></td>
<td></td>
<td>232.5</td>
<td>202.5*</td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td>97.427</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td>32.395</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td>23.96</td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>103</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>= 8</td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
STANFORD MEDICAL CENTER
PATIENT No.5

3:05am 5/29/96  MODS SCORE = 7
PO2 = 131
FIO2 = 0.3
Serum Creatinine = 53.142 umol/L
Serum Bilirubin = 206.305 umol/L
HR = 126
CVP = 8
MAP = 88
Platelet Count = 223

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td>436.66</td>
<td>243.33*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(PO2 / FIO2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td>53.142</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Serum Creatinine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td></td>
<td>206.30</td>
<td></td>
</tr>
<tr>
<td>(Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td>11.45</td>
<td></td>
</tr>
<tr>
<td>(HR x CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td>223</td>
<td></td>
<td></td>
<td>75*</td>
<td></td>
</tr>
<tr>
<td>(Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td>/</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
FI02 = 0.5
Serum Creatinine = 97.427 umol/L
Serum Bilirubin = 153.45 umol/L
HR = 101
CVP = 7
MAP = 76
Platelet Count = 55

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2/FI02)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>190</td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td>97.427</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>153.45</td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td>9.30</td>
<td></td>
<td></td>
<td>15.03*</td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>55</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>= 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
3:05 am 6/7/96  MODS SCORE = 11
PO2 = 78
FiO2 = 1.0
Serum Creatinine = 168.283 umol/L
Serum Bilirubin = 81.84 umol/L
HR = 116
CVP = 11
MAP = 95
Platelet Count = 124

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td></td>
<td></td>
<td></td>
<td>78</td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td></td>
<td></td>
<td>168.283</td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td>81.84</td>
<td>126.17*</td>
</tr>
<tr>
<td>Cardiovascular (HR x CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td>13.29</td>
<td>16.17*</td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td>124</td>
<td>74*</td>
</tr>
<tr>
<td>Neurologic (glascow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td>= 11</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
3:00 am 69/96 MODS SCORE = 5
PO2 = 124
FiO2 = 0.30
Serum Creatinine = 88.57 umol/L
Serum Bilirubin = 75.02 umol/L
HR = 109
CVP = 6
MAP = 83
Platelet Count =

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td>413.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td>88.57</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td>75.02</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td>7.66</td>
<td>811.33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80*</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TOTAL SCORE

* Denotes previous worst organ score
4:11 am 7/5/97  MODS SCORE = 3

P02 =
FIO2 = 0.3
Serum Creatinine = umol/L
Serum Bilirubin = umol/L
HR = 128
CVP = 14
MAP = 78
Platelet Count = 41

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FIO2)</td>
<td></td>
<td></td>
<td>207.5*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td></td>
<td>115.41*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td>260.855*</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td>22.97</td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>41</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
4:30 am 7/7/96 MODS SCORE = 14  
P02 = 68  
FiO2 = 1  
Serum Creatinine = 177.14umol/L  
Serum Bilirubin = 225.06umol/L  
HR = 139  
CVP = 11  
MAP = 81  
Platelet Count = 46

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>TOTAL SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (P02 / FiO2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>68</td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td></td>
<td></td>
<td>177.14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>225.06</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR x CVP / MAP)</td>
<td>18.87</td>
<td></td>
<td></td>
<td></td>
<td>25.20*</td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>45</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
</tbody>
</table>
2:25 am 12/16/96  MODS SCORE = 8
P02 = 113
FIO2 = 0.4
Serum Creatinine = 70.856 umol/L
Serum Bilirubin = 18.755 umol/L
HR = 97
CVP = 13
MAP = 80
Platelet Count = 137

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>RESPIRATORY (P02 / FIO2)</td>
<td></td>
<td></td>
<td></td>
<td>282.5</td>
<td></td>
</tr>
<tr>
<td>RENAL (Sr. Creatinine)</td>
<td>70.856</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEPATIC (Sr. Bilirubin)</td>
<td>18.755</td>
<td>34.1*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARDIOVASCULAR (HR X RAP / MAP)</td>
<td>15.76</td>
<td></td>
<td>22.90*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HEMATOPOETIC (Platelet Count)</td>
<td>137</td>
<td></td>
<td></td>
<td>46*</td>
<td></td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td>= 8</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
3:50 am 12/28/96 MODS SCORE = 16
P02 = 115
FIO2 = 0.7
Serum Creatinine = 309.995umol/L
Serum Bilirubin = 160.27umol/L
HR = 145
CVP = 25
MAP = 77
Platelet Count = 32

<table>
<thead>
<tr>
<th>ORGAN SYSTEM</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (P02 / FIO2)</td>
<td></td>
<td></td>
<td>164.28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td></td>
<td></td>
<td>309.995</td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>160.27</td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>47.07</td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td>32</td>
<td>20*</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td>≈ 16</td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
2:55 am 12/31/96 MODS SCORE = 7
PO2 = 128
FiO2 = 0.3
Serum Creatinine = 124 umol/L
Serum Bilirubin = 465 umol/L
HR = 102
CVP =
MAP = 85
Platelet Count = 331

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td></td>
<td></td>
<td></td>
<td>427</td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td></td>
<td></td>
<td>124</td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>465</td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td>18.4*</td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td>331</td>
<td></td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
3:15 am 1/18/97  MODS SCORE = 3
PO2 = 123
FiO2 = 0.4
Serum Creatinine = 88.6 umol/L
Serum Bilirubin = 63 umol/L
HR = 123
CVP = 8
MAP = 67
Platelet Count = 288

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td></td>
<td>307</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td>88.6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR x CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.3</td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>288</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td>=3</td>
<td></td>
</tr>
</tbody>
</table>
2:50 am  2/19/97    MODS SCORE = 6
PO2 = 77
FiO2 = 0.35
Serum Creatinine = 124 umol/L
Serum Bilirubin = 39 umol/L
HR = 120
CVP = 7
MAP = 78
Platelet Count = 180

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
<td></td>
<td>220</td>
<td></td>
</tr>
<tr>
<td>(PO2 / FiO2)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal</td>
<td></td>
<td></td>
<td>124</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Serum Creatinine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic</td>
<td></td>
<td></td>
<td>39</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td>10.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(HR X CVP / MAP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic</td>
<td></td>
<td></td>
<td>180</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>6</td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
12:50 am 4/22/97  MODS SCORE = 5
PO2 = 129
FiO2 = 0.35
Serum Creatinine = 71 umol/L  CICr = 87
Serum Bilirubin = 73 umol/L
HR = 91
CVP = 9
MAP = 59
Platelet Count = 92

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td></td>
<td>369</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td></td>
<td></td>
<td>71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td></td>
<td></td>
<td></td>
<td>73</td>
<td>121*</td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td>8.3</td>
<td>92</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92</td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>= 5</td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
8:10 am  4/30/97  MODS SCORE = 10

PO2 = 128
FiO2 = 0.56
Serum Creatinine = 142 umol/L  
CLCr = 81 / 64 Adjusted
Serum Bilirubin = 17 umol/L
HR = 73
CVP = 16
MAP = 98
Platelet Count = 239

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (PO2 / FiO2)</td>
<td>229</td>
<td></td>
<td>195*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td>142</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hepatic (Serum Bilirubin)</td>
<td>17</td>
<td>26*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td>11.9</td>
<td>182*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td>239</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>= 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
1:10 am  5/17/97  MODS SCORE = 6
P02 = 79
FIO2 = 0.35
Serum Creatinine = 71 umol/L    CLCr = 144 / 111 Adjusted
Serum Bilirubin = 26 umol/L
HR = 76
CVP = 10
MAP = 86
Platelet Count = 101

<table>
<thead>
<tr>
<th>Organ System</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory (P02 / FIO2)</td>
<td></td>
<td>226</td>
<td>174*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal (Serum Creatinine)</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hapatic (Serum Bilirubin)</td>
<td></td>
<td>26</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular (HR X CVP / MAP)</td>
<td>8.8</td>
<td></td>
<td>10.2*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hematologic (Platelet Count)</td>
<td></td>
<td></td>
<td></td>
<td>101</td>
<td></td>
</tr>
<tr>
<td>Neurologic (glasgow)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>TOTAL SCORE</td>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Denotes previous worst organ score
Bibliography


