A Prospective Study of the Incidence and Predictive Value of Myocardial Markers in Septic Shock

Dennis Kelly

A. Introduction

Septic shock is a leading cause of death in intensive care units.[1] Its incidence is increasing and gram negative sepsis has increased tenfold in the last ten years resulting in the death of approximately 150,000 Americans annually.[2] In general mortality rates vary between 20 and 80%. [3]. Reported mortality rates vary considerably in part due to the absence of universally agreed upon definitions, a problem that was addressed earlier in this decade.[4] Sepsis is the physiologic response to infection in the blood or tissues. Manifestations include hyperthermia or hypothermia, tachypnea or tachycardia. Severe Sepsis is sepsis associated with organ dysfunction, hypoperfusion abnormality, or sepsis induced hypotension. Typical manifestations of end organ hypoperfusion include change in level of consciousness, lactic acidemia, oliguria, or unexplained hypoxemia or coagulopathies. Septic Shock is a subset of severe sepsis involving sepsis induced hypertension persisting despite adequate fluid resuscitation, along with the presence of hypoperfusion abnormalities and oraan dysfunction.[5] The increase in incidence of sepsis and septic shock has been, in part, attributed to increased use of cytotoxic and immunosupressive drugs, increased patient age, antibiotic resistant organisms, and the use of more invasive devices for diagnosis and therapy.[6] Death in patients with septic shock is thought to be a result of one of the following processes: refractory hypotension by peripheral vasodilation unresponsive to vassopressors, myocardial depression, or multiple -organ system failure. [7]

The myocardial depression accompanying septic shock has been the subject of much study. The working definition of septic shock used for most of these studies, however, more closely matches the concensus panel definition of severe sepsis. The subjects usually had manifestations of sepsis and hypotension. This is a complex form of shock referred to distributive shock where there is arterial and venous dilation and increased extravasation of fluids leading to low systemic resistance and, provided there is adequate fluid resuscitation to compensate for the increased vascular space, cardiac output is normal or above normal. Although cardiac output is normal or above normal, ventricular function is markedly abnormal. Radionucleotide gated blood-pool scanning and simultaneous thermodilution hemodynamic measurements have revealed that myocardial performance in this state is characterized by reduced left ventricular and right ventricular ejection fractions with increased end diastolic volume in each ventricle, and pulmonary hypertension[8]

There have been several hypotheses regarding the mechanism of myocardial dysfunction. Animal models of endotoxinernia had suggested global myocardial ischemia as a cause for myocardial depression. Cunnion and associates studied seven patients with septic shock using a pulmonary artery catheter, Radionucleotide scanning, and a coronary sinus catheter. Coronary blood flow and myocardial oxygen extraction were found to be normal and they also found a net lactate extraction in the coronary vascular bed (use of lactate requires oxygen).[9] Dhainaut and associates use a PA catheter and a coronary catheter to investigate 40 patients with septic shock. Patients with coronary artery disease were excluded. Coronary blood flow was found to increased in the majority of these patients as was myocardial lactate extraction. There were 6/40 patients who had evidence of ischemia which argues against ischernia as the primary cause of myocardial depression.[10]

A second hypothesis which was first postulated more than 20 years ago is that there are circulating myocardial depressant substances in patients with septic shock. When serum obtained from patients during the acute phase of shock is incubated with myocardial cells from newborn rats, the extent and velocity of myocardial shortening is impaired compared to the myocardial performance observed when these myocardial cells are incubated with the serum of normal subjects, the serum of those with

other critical care requiring conditions, the serum of those with structural heart disease.[11] Further study has demonstrated that patients who have this myocardial depressant substance in their serum have lower ejection fractions, larger end diastolic volumes, higher pulmonary wedge pressures, higher peak lactate concentrations, and higher mortality rates (36% vs 10%) than those without such activity in their serum. [12] The responsible substance has not been isolated, however, TNF produces a myocardial shortening and recent work suggests that the synergistic action of TNF-A1pha and IL-1-Beta. [13]

Remarkably, there have been no reports in the literature of myocardial enzyme measurement in these patients. Although myocardial dysfunction is observed to be reversible in those that survive, this does not preclude the possibility of global myocardial cell injury in these patients which might well be manifested by elevation of myocardial enzymes such as Creatine Kinase MB and Troponin I or T. Those who do not survive may well be victims of irreversible myocardial injury which may be manifest by elevation of myocardial enzymes. Measurement of myocardial enzymes might be of significant value in determining prognosis. The study by Dhainaut and associates demonstrates that while ischernia is not likely the primary mechanism of myocardial depression, a significant number of patients 6/40 (15%) of patients had evidence of ischemia in spite of exclusion of patients with coronary artery disease from the study. Identification of these patients might be useful in defining a different prognostic subgroup which may respond well to optimization of hemodynamics or to anti-ischemic therapies though options in setting of hypotension are limited. If ongoing myocardial damage was observed to correlate with myocardial depression, it will likely have implications in future pathophysiologic studies of this disease entity and the prognosis of survivors of septic shock.

The importance of detection of myocardial injury in the ICU setting is underscored by a study by Guest and associates which sought to determine the incidence of unrecognized cardiac injury in critically ill patients by measuring Cardiac Troponin I daily in all patients admitted to a medical ICU.14 They found evidence of myocardial damage based on elevated Troponin I levels in 32 of 209 patients (15%). Only 12 (37%) of these patients were diagnosed as having myocardial infarction by the ICU staff. Mortality in patients with myocardial injury, detected (42%) or undetected (40%) was significantly higher than in those without myocardial injury (15%)($P<.001$). These patients had significantly more hypotension, were more apt to be on ventilator, and had longer ICU stays than those without myocardial damage. The frequency of elevated troponin I values by diagnosis was higher for sepsis 5/16 (31%) than for any other admitting diagnosis except for cardiopulmonary arrest suggesting frequent occurrence of cardiac damage in septic patients.

B. References

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Lay Summary

A Prospective Study of the Incidence and Predictive Value of Myocardial Markers in Septic Shock

Dennis H. Kelly--Department of Medicine

Study Purpose

Septic Shock is a severe manifestation of infection resulting in low blood pressure and reduced blood flow to one or more vital organ systems often resulting in failure of one or more organ systems and high mortality rates (40% - 60%). One of the features of this complex condition is reduced contraction of the heart. The condition of septic shock is thought to cause a heart depressing substance to become present in the blood which is thought to be responsible for the reduced contractility of the heart. No study can be found in which markers of heart cell injury such as creatine kinase MB, myoglobin, or newer markers such as serum troponin I have been measured in these patients. A study in which troponin I was measured in approximately 200 admissions to a medical ICU excluding admissions for cardiac diagnosis found elevation of this marker in 15% of the patients with a higher mortality rate in these individuals (40% vs. 15%). When analyzed by diagnosis, the incidence of troponin I elevation was among the highest at 5/16 (3 1 %). I propose to measure creatine kinase MB, myoglobin, and troponin I in patients with septic shock to measure the incidence of marker elevations in this population and the utility of these measurements with regard to prediction of mortality.

Study Design

A Prospective Study of the Incidence and Predictive Value of Cardiac Enzymes Elevations in Patients with Severe Sepsis

I propose to measure CK-MB, Myoglobin, and Troponin I in patients with septic shock at the time of admission to the MICU, CCU, or SICU and the morning after admission in order to assess the incidence of elevated levels of these enzymes in these patients and to determine the prognostic significance of these enzymes in this population. Other variables will be monitored such as length of ICU stay, length of stay in hospital, duration of vasopressors, source of sepsis, identification of infecting organism, presence of EKG changes, occurrence of chest pain, presence of heart failure, and presence of arrythmias in order to assess the implications of cardiac damage as indicated by myocardial enzymes and in order to draw inferences for further study. Demographic variables include age, sex, chronic medical diseases, risk factors for heart disease including family history, hypertension, hypercholesterolemia, tobacco use, presence of diabetes mellitus, history of myocardial infarction, history of angina, history of coronary artery disease, and history of structural heart disease will be monitored and analyzed for differences in those who have an elevated cardiac markers vs. those who do not. All qualitative variables will be analyzed by Chi-squared tests, except where small sample size requires the use of the Fishers Exact test. Quantitative variables will be analyzed by the Wilcoxon Rank sum Test because of non-normal distribution.

Subjects

We anticipate enroll i n g 100 adult subjects of all ages and races, both male and female.

Adult Patients of all ages, races, both male and female, who present to the MICU, CCU, or SICU with a history and physical suggestive of sepsis will be considered for study. Initial diagnosis of sepsis will be made if more than 1 of the following criteria are met: (1) hyperthermia >38 degrees Celsius or hypothermia <36 degrees Celsius: (2) Heart rate > 90 beats/min; (3) White cell count < 4,000/mL or > 12,000/mL; (4) clinical evidence of infection (i.e. positive blood culture. A diagnosis of septic shock will be made and patients will be recruited for the study when the following criteria are met: Sepsis with hypotension unresponsive to adequate fluid resuscitation (<90mm Hg systolic or a decrease of >40 mm Hg from baseline); presence of perfusion abnormalities or organ dysfunction that may include, but are not

I imited to, lactic acidosis, oliguria, or an acute alteration of mental status. There will be no exclusion of groups at higher risk for more severe disease such as those with AIDS or other causes of inimnosuppression. There will be no exclusion of patients with a history of coronary artery disease. One might anticipate that the inclusion of these groups will result in a greater incidence of myocardial enzymes. I feel that that inclusion of these groups will result inclusion of a group of patients that are representative of patients presenting with sepsis and will help identify groups in whom measurement of cardiac enzymes routinely may be of utility. Cardiac injury in the group with coronary artery disease may be different mechanistically than it is in the rest of the patients. All races and both sexes shall participate in the study.

100 patients will participate in the study assuming an incidence of elevated Troponin I of 30% and an increase in mortality rate of 25%.

Recruitment Method

Adult patients meeting the criteria detailed in part G of this document will be recruited by the ICU teams caring for the patients.

Study Procedures

Participating patients will have approximately 5 cc of blood drawn upon admission to the MICU, CCU, or SICU and again the following morning. Demographic variables detailed in Section G wil I be obtained by review of the chart and history from patients or their families. The patients chart will be monitored throughout their stay clinical events as detailed in section G.

Issues

There are no ethical or physical risk concerns.

IRB PROTOCOL

A. Purpose and Rationale Septic

Shock is a severe manifestation of infection resulting in low blood pressure and reduced blood flow to one or more vital organ systems often resulting in failure of one or more organ systems and high mortality rates (40% - 60%). One of the features of this complex condition is reduced contraction of the heart. The condition of septic shock is thought to cause a heart depressing substance to become present in the blood which is thought to be responsible for the reduced contractility of the heart. No study can be found in which markers of heart cell injury such as creatine kinase MB, myoglobin, or newer markers such as serum troponin I have been measured in these patients. A study in which troponin I was measured in approximately 200 admissions to a medical ICU excluding admissions for cardiac diagnosis found elevation of this marker in 15% of the patients with a higher mortality rate in these individuals (40% vs. 15%). When analyzed by diagnosis, the incidence of troponin I elevation was among the highest at 5/16 (31%). I propose to measure creatine kinase MB, myoglobin, and troponin I in patients with septic shock to measure the incidence of marker elevations in this population and the utility of these measurements with regard to prediction of mortality.

B. Study Design and Statistical Analysis

I propose to measure CK-MB, Myoglobin, and Troponin I in patients with septic shock (detailed description in Section G) at the time of admission to the MICU, CCU, or SICU and the morning after admission in order to assess the incidence of elevated levels of myocardial markers in these patients and to determine the prognostic significance of these enzymes in this population. Other varhi bl es will be monitored such as, length of ICU stay, length of stay in hospital, duration of vasopressors, source of sepsis, identification of infecting organism, presence of EKG changes, occurrence of chest pain, presence

of heart failure, and presence of arrythmias in order to assess the implications of cardiac damage as indicated by myocardial-6-5-2ymes and in order to draw inferences for further study. Demographic variables include age, sex, chronic medical diseases, risk factors for heart disease including family history, hypertension, hypercholesterolemia, tobacco use, presence of diabetes mellitus, history of myocardial infarction, history of angina, history of coronary artery disease, and history of structural heart disease will be monitored and analyzed for differences in those who have an elevated cardiac markers vs. those who do not. All qualitative variables will be analyzed by Chi-Squared Tests, except where small sample size requires the use of the Fishers Exact Test. Quantitative variables will be analyzed by the Wilcoxon Rank Sum test because of an anticipated non-normal distribution.

C. Study Procedures

Participating patients will have approximately 5 cc of blood drawn upon admission to the MICU, CCU, or SICU and again the following morning. Given the critical nature of Septic Shock these patients will have an arterial line placed (a standard of clinical care) by the ICU staff for continuous monitoring and access to blood. No further catheter placement is required for this study and Wood draws will be painless and rapid using arterial line access.

D. Study Drugs

No Medications are to be received as part of the protocol. These patients will be on an antibiotic regimen and other medications in keeping with standard medical care as specified by the ICU team caring for these patients.

E. Medical Devices

No use of any devices is specified by this study.

F. Study Questionnaires

No questionnaires are to he utilized In this Study. All data will be acquired by the principal investigator

G. Description of the Subjects and Method of Recruitment

Patients who present to the MICU, CCU, or SICU with a history and physical suggestive of sepsis will be considered for study. Initial diagnosis of sepsis will be made if more than 1 of the following criteria are met: (1) hyperthermia >38 degrees Celsius or hypothermia <36 degrees Celsius: (2) Heart Rate > 90 beats/min; (3) White cell count < 4,000/mL or > 12,000/mL; (4) clinical evidence of infection (i.e. positive blood culture. A diagnosis of septic shock will be made and all patients will be recruited for the study when the following criteria are met: Sepsis with hypotension, unresponsive to adequate fluid resuscitation (<90mm Hg systolic or a decrease of >40 mm Hg from baseline); presence of perfusion abnormalities or organ dysfunction that may include, but are not limited to, lactic acidosis, oliguria, or acute alteration of mental status. There will be no exclusion of groups at higher risk for more severe disease such as those with AIDS or other causes of immnosuppression. There will he no exclusion of patients with a history of coronary artery disease. One might anticipate that the inclusion of these groups will result in a greater incidence of myocardial enzymes. I feel that that inclusion of these groups will result inclusion of' a group patients that are representative of patients presenting with sepsis and will help identify groups in whom measurement of cardiac enzymes routinely may be of utility. Cardiac Injury in the group with coronary artery disease may be different mechanistically than it is in the rest of the patients. All races and both sexes shall participate in the study.

Participants In this study likely will have in altered mental status and therefore many participants will not be able to give consent. We will attempt to identify participants early in the course of illness in order in obtain consent when possible. If the patient is not in condition to consent, consent will he obtained from family members. Fortunately, this study brings almost no risk to the paitent.

100 patients will participate in the study assuming an incidence of elevated Troponin I of 30% and an increase in mortality rate of 25%.

H. Confidentiality

The results of the blood tests will not be reported on the clinical information service and will be available only to the principle investigator and collaborating laboratory personnel. The samples will be coded so that no identifiers such as unit numbers, social security numbers, phone numbers, name and etc. so that non-participants in the study would not be able to access data traceable to a specific patient..

I. Location

CCU, MICU and SICU in the Milstein Pavilion.

J. Risks and Benefits

There is virtually no added risk to the patient as total blood requirements for the study do not exceed 10 cc. The study will he of no benefit to the participating subjects, however, the study results may result in improved understanding of myocardial depression in septic patients or help identify a subset of patients vulnerable to cardiac complications or patients with a worse prognosis in whom care might be optimized in one way or another.

K. Alternative Therapies

Not relevant to this study as no therapy is specified by the protocol.

L. Compensation and Costs to Subjects

There will be no costs or compensation to subjects.

M. Minors and Research Subjects

No minors are to be enrolled in the study.

N. Radiation or Radioactive Substances

No procedures or utilizing radiation or radioactive substances are specified by the study.