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PHYSIOLOGIC, MATABOLIC AND MEDIATOR RESPONSES IN POSTTRAUMA ARDS AND SEPSIS: IS OXYGEN DEBT A CRITICAL INITIATING FACTOR?

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Posttrauma adult respiratory distress syndrome (ARDS) and sepsis initiate complex humoral and cellular inflammatory responses that initially effect the microvascular system, but rapidly extend to involve and modulate the solid organ metabolic response. It is discussed whether the interaction between these cellular processes and the organs which they involve appear to be initiated by the trauma induced oxygen debt.

Key words: *trauma, sepsis, oxygen debt, acute respiratory distress syndrome, oxidative metabolism.*

INTRODUCTION

Investigators in the field of shock and trauma have long pursued the initiating factors and their sequelae which lead to the normal and pathophysiologic host defense responses. An adequate host defense response to trauma or hemorrhage leads to a sequence of compensation which successfully permits the host to withstand the traumatic insult and its related hypovolemic shock without the subsequent development of an exaggerated host define response which may lead to excessive inflammatory organ dysfunction, such as the adult respiratory distress syndrome (ARDS), or an inadequate host defense response which predisposes the individual to the development of invasive bacterial sepsis. There are many factors which influence the course of injury recovery after the intiation of traumatic shock. However, recent studies suggest that the critical initial event which sets the nature and adequacy of the initial host defense response is related to the forced reduction in perfusion which

limits oxygen delivery (1). When delivery of oxygen to the tissues falls below the level of the mandatory level of cellular oxygen consumption, oxidative metabolism becomes impaired and then ceases. The difference between the oxidative needs and the oxygen delivery is known as the oxygen debt and the appearance of an oxygen debt is associated with the induction of cellular anaerobic metabolism.

The concept of oxygen debt

Estimation of the presence and the magnitude of hypovolemic shock-induced, oxygen debt generated anaerobic metabolism is difficult in man. However, recent studies (2, 3) have suggested that a quantification of the magnitude of the oxygen debt can be made by examining the plasma levels of those metabolic variables which reflect the ischemic consequences of anaerobic metabolism.

Under ordinary circumstances glucose is the major metabolic fuel which is metabolized to produce a positive energy balance. However, when tissue oxygen delivery is reduced below the level of oxygen consumption (oxygen debt), the oxidation of glucose ceases, as oxygen fixation along the cytochrome electron chain is interrupted. Consequently, transport into the mitochondrial tricarboxylic acid cycle of the two three-carbon fragments of a glucose molecule produced by the glycolytic cycle is prevented at the level of pyruvate dehydrogenase [PDH] (4). As a result, pyruvate and its disequilibrium product lactate are increased in the cell cytosol (4, 5). When this occurs, lactate which easily passes across the cell membrane is increased in the blood plasma. Lactic acidemia is present in postraumatic hypovolemia regardless of the level of blood pressure when muscle neds, liver and kidney are hypoperfused below the critical level of flow related oxygen delivery.

In addition, the activity of a wide range of enzymatic systems which are responsible for the oxidation of substrates other than glucose also becomes arrested and the production of oxygen derived energy sources (primarily as adenosine triposphate (ATP) and related compounds) is reduced. As a consequence amino acids, especially the gluconeogenic amino acids involved in the glucose-energy transport system from muscle to liver (alanine, glycine, etc) and other more complex metabolic acids also accumulate in the plasma (6). The continuing requirement for high energy phosphate compounds to sustain aerobic metabolism and membrane integrity (primarily ATP), results in a net degradation of ATP into lower energy adenosine diphosphate (ADP) and monophosphate (AMP), and finally to phosphoric acid (PO_4). These products added to the lactic acidemia contribute to the total metabolic acidosis found as a consequence of the oxygen debt caused by the hypovolemia-induced hypoperfusion.

As the magnitude of the oxygen debt increases and since viable animal cells under normothermic conditions are unable to cease metabolism without death, the oxygen debt progresses and the total of all of the metabolic acids in the intra and extracellular water increases producing progressive ischemic acidosis. This overhelms the buffering capacity of the blood and is reflected in the net metabolic acidosis, known clinically as the base deficit (negative base excess). Since the base deficit reflects all the metabolic acids (7), it rises more rapidly in the blood plasma than does lactate acid and continues to rise to a higher level. As a result, both the base deficit and the level of lactic acidemia become sensitive indicators of the magnitude of the oxygen debt induced by the ischemia.

If resuscitation is begun and successfully achieved before critical levels of oxygen debt produce cell death, the reperfusion of organs with oxygen carrying blood allows a reinstitution of cellular oxidative phosphorylation. The various anaerobic metabolic acids including lactate are oxidized to CO_2 and H_2O with reconstitution of high energy phosphates, such as ATP, from their lower energy products (ADP and AMP). As a result the fall in the blood levels of the metabolic parameters of anaerobic metabolism provides a sophisticated method by which the clinician can quantify the rate and magnitude of the repayment of the ischemic oxygen debt (O_2 debt). The concept of an ischemia induced oxygen debt and its three possible consequences are shown in *Fig. 1.*

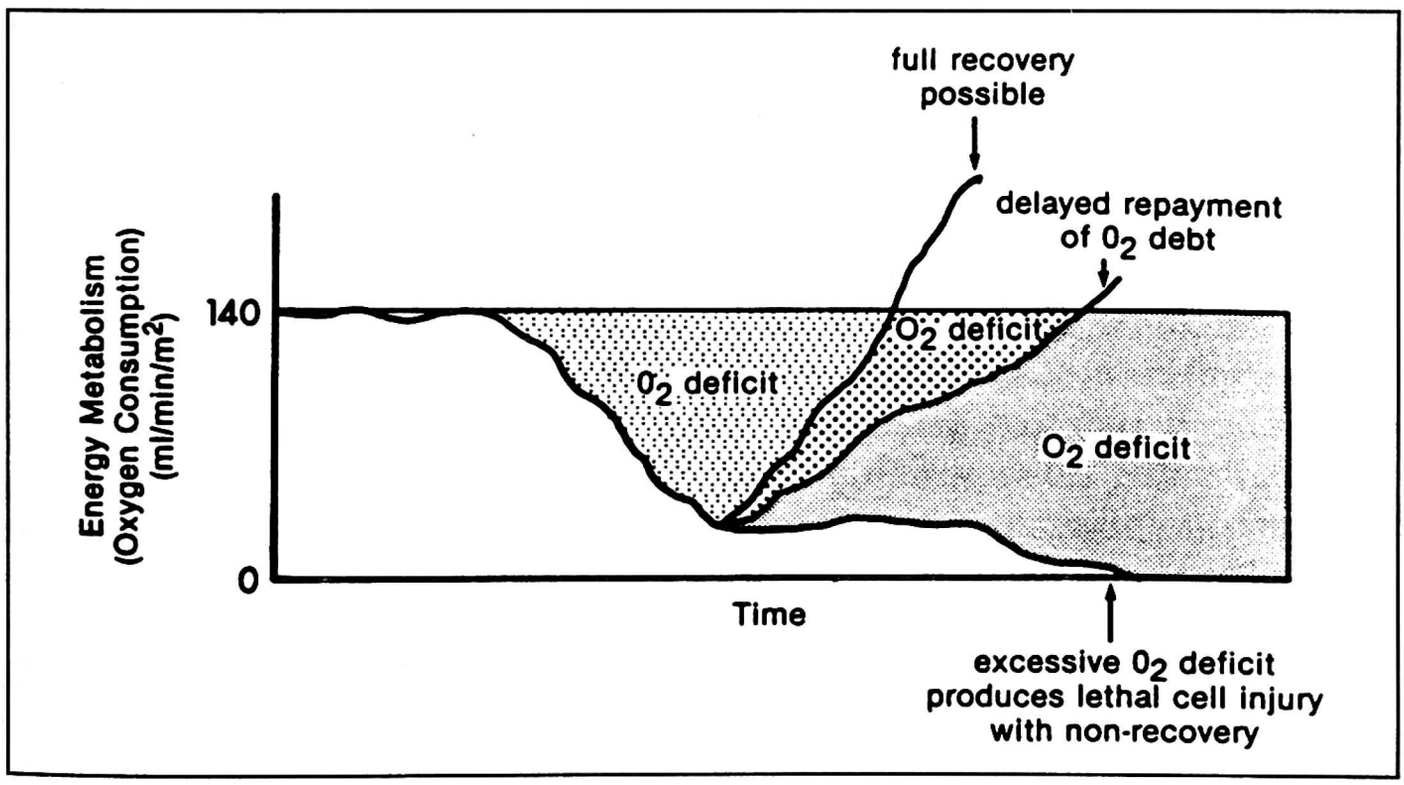

Fig. 1. Conceptual Modes of Oxygen Debt. From Siegel JH, Linberg SE, Wiles CE. Therapy of low flow shock states. Siegel JH (ed) Trauma: Emergency Surgery and Critical Care. Churchill Livingston New York London 1987; 201—284.

As oxygen consumption drops below the critical baseline level energy metabolism is reduced and oxygen deficit accumulates. When volume resuscitation is instituted, tissue perfusion increases and the oxygen debt is repaid. However, during the period of hypoperfusion there is liberation of a variety of shock mediators which have the capability to increase basal metabolism. As a result, not only must the deficit be repaid in full, but there is also an increase in the rate of key metabolic responses during the period immediately after the oxygen deficit phase is repaid. Consequently, there is an increase in total body oxygen consumption which rises above the preshock baseline level during the immediate post-resuscitation period. This heightened metabolic response is accompanied by a mandatory increase in the cardiovascular response producing a rise in the cardiac output, which is usually associated with a fall in peripheral vascular resistance. This latter phenomenon also appears to be related to shock-mediator induced arterial relaxation during the O_2 repayment phase. This complex cardiovascular and metabolic response is known as the post-traumatic hyperdynamic state (8).

The oxygen debt induced mediator response

If the oxygen debt is not repaid within a critical period of time, intracellular mechanisms are activated which initiate lysosomal auto-destruction and cell death occurs (9). This prevents a reconstitution of cellular energy metabolism even though whole body perfusion is restored. In this instance, a lethal outcome occurs, without an increase in oxygen consumption. As an intermediate consequence of a less severe oxygen debt, but one which is associated with delayed repayment beyond a critical level of metabolism, there is a greater degree of damage to more oxygen dependent cells than to others which are more resistant to O_2 debt. In some instances the oxidative repletion of ATP appears to result in the activation of a variety of specialized genes which lead to the reprioritization of protein synthesis and may also result in the down regulation of key enzyme systems. In particular there is evidence that activation of apoptosis genes may occur, which in turn leads to programmed cell death at a subsequent time (10).

The concept is that if the oxygen debt is allowed to increase above a critical threshold level, it will set in motion a variety of destructive intracellular processes, there in turn result in the local elaboration and then the systemic liberation of superoxides, eicosanoids and intracellular proteases (11—16). Thus, it is not merely the achievement of an acccelerated rate of repayment of an oxygen debt, but also its limitation to below a critical threshold level which are the goals to be achieved by early and effective resuscitation. Failure to control the hypovolemic oxygen debt initiates the activation of destructive superoxide by-products, such as peroxynitrates, hypochlorous acids and

hydroxyl ions, which are generated with return of oxygen to previously ischemic vascular beds causing a reperfusion injury.

This reperfusion injury first effects the vascular endothelial cells in the area of previous ischemia as the ATP breakdown product of hypoxanthine is oxidized by xanthine oxidase (13). However, these superoxide byproducts if produced in excess will eventually result in injury or death of parenchymal cells, not only within the region of the reperfused vasculature, but also in organs at some distance from the area of ischemia. This latter dissemination of the oxygen debt injury is initiated by a variety of mediators generated by the reperfusion of previously ischemic vascular beds. These include the liberation of eicosanoids liberated from damaged cell membranes (14). The membrane activation of phospholipase A_2, most prominently produces the generation of a variety of leukotrienes *via* the lipoxygenase pathway. These compounds induce leukocyte degranulation of proteases, activation of leukocyte superoxide potential by the initiation of increased myloperoxidase activity, and most importantly, they cause the initiation of selectin and integrin proteins on the surface of both leukocytes and endothelial cells (see 11&12 for review). These in turn induce adherence of the leukocyte to the endothelial surface where the release of the leukocyte proteases and superoxides eventually cause disruption of the endothelial membrane with an increase in vascular permeability (15, 16). This break in the continuity of the vascular endothelium permits leukocyte invasion of the underlying interstitium in the area of vascular injury. Leukotrienes and other eicosanoids also initiate monocyte and macrophage induction of protein cytokines and these activated cells and their mediators carried by the circulating blood also extend the vascular inflammatory response to areas remote from the initial ischemic injury (11, 12). The macrophage synthesized cytokines also transduce functional alterations in the intermediary metabolism of structural cells within body organs, most notably in skeletal muscle, liver, pancreatic endocrine, and in some instances neurologic cells (17). There is evidence that some cytokines also cause the initiation of increase nitric oxide production by activating inducible nitric oxide synthetase (INOS) and this endothelial relaxing mediator is thought to play a critical role in producing peripheral vascular vasodilation (18).

Other eicosanoids of the cyclooxygenase pathway initiate thrombosis of small vessels through activation of thromboxane in areas of injury and increase microvascular permeability (19), as well as causing increased vasodilator activity increasing blood flow into the periphery of the traumatized area through activation of PGI_2. Finaly the cyclooxygenase pathway plays a major role in the liberation of universal immune-suppressant, PGE_2 (20). The important aspect of this complex of eicosanoid, cytokine, nitric oxide humoral and leukocyte-macrophage cellular responses is that under circumstances of severe oxygen debt which passes a critical threshold levels, not only do the

inflammatory components of this response become excessively unbalanced, but the immune-suppressant aspecta initiated by PGE_1 and possibly by anti-inflammatory cytokines may also become a negative factor. This opens the way for both an exaggerated host defense response with vital organ autodestruction, the „host defense failure syndrome" producing multiple organ dysfunction. At the same time as there is stimultaneously produced immune paresis and which may reduce the ability to combat invasive bacterial and viral infections, leading to aggressive and uncontrolled septic processes (11, 12).

Quantification of oxygen debt

The relationship of the oxygen debt accumulation to volume loss is shown in *Fig. 2* (3) which demonstrates that sham reductions in blood volume up to 30% may produce only minimal increases in oxygen debt, since the major

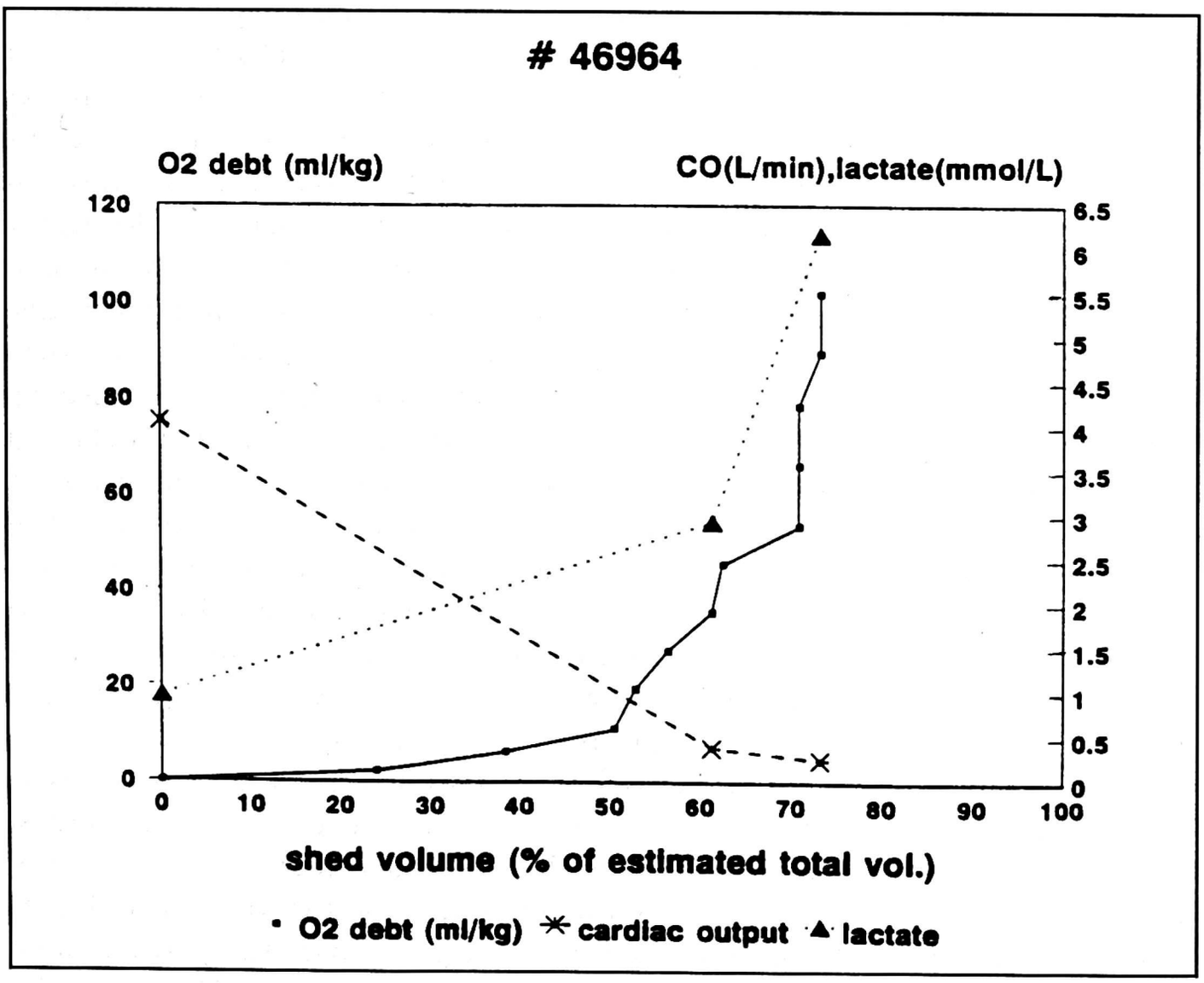

Fig. 2. Relatiom of blood volume loss to O_2 debt accumulation and mean blood pressure fall in a 24.4 kg dog. Estimated blood volume 2, 123 mL; blood volume withdrawn 1552 mL 73.1% of estimated blood volume removed at 60 minutes; each point corresponds to a sequential 5-minute time. From Siegel, Fabian, Smith, Costantino (3).

organs which are underperfused at this level of hypovolemia are those which already have supplies of long-acting high energy phosphates, such as the creatine phosphate found in skeletal muscle. However, once blood volume reduction passes a critical point, then cardiac output (CO) and tissue perfusion falls and the oxygen debt rises in an exponential fashion, as is also shown in *Fig. 2.* This rapid increase in oxygen debt reflects the point of underperfusion of critical organs, such as liver, kidney, brain and eventually heart. This exponential phase of oxygen debt is associated with a parallel rapid rise in blood lactate and a fall in base-excess producing an increased base deficit 2, 3).

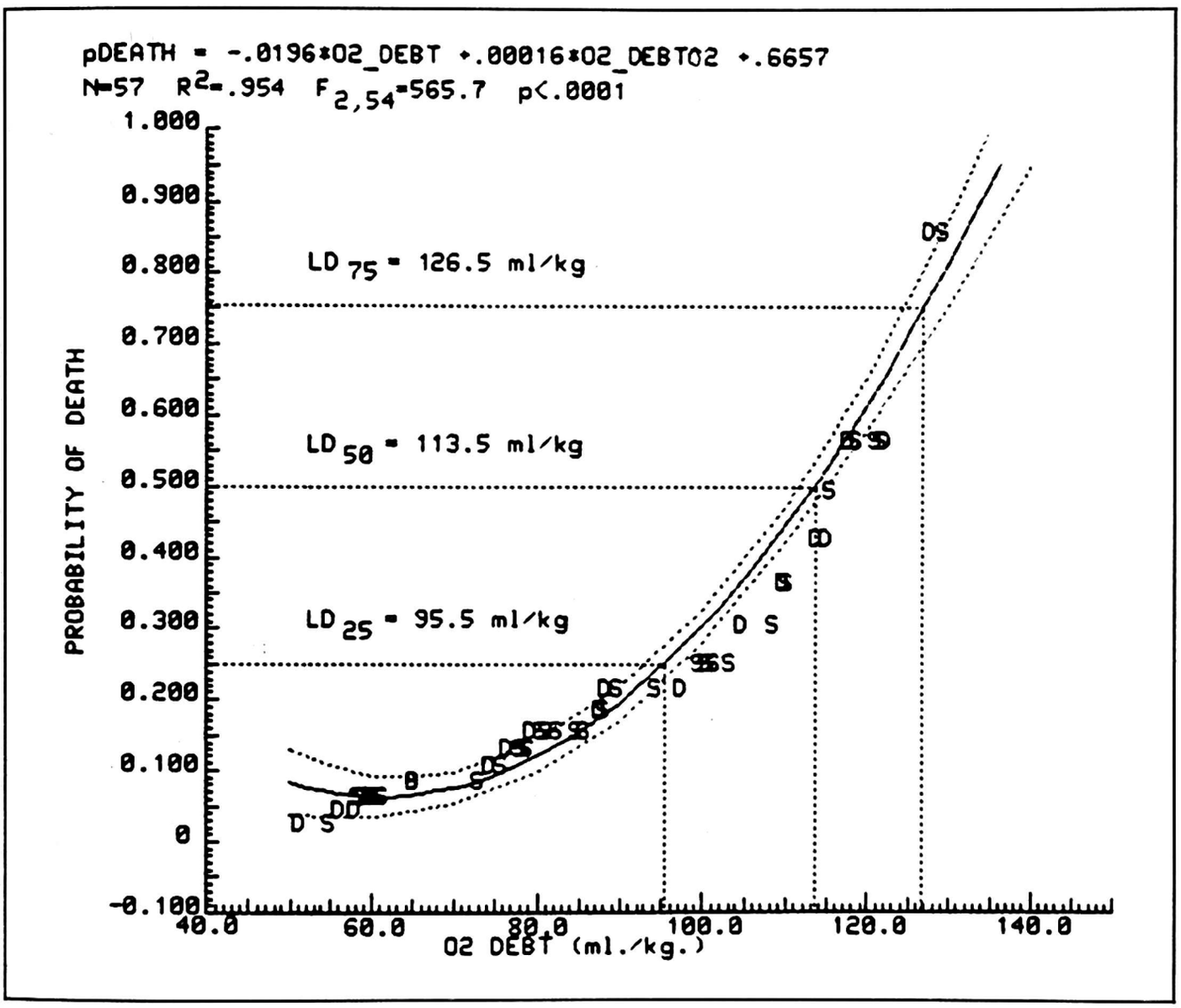

Fig. 3. Relationship of probability of death to O_2 debt, canine data. From Dunham, Siegel, Weireter, Fabian (2).

While the processes set into action by the accumulation by an oxygen debt are complex and are associated with cellular responses in virtually every bidy system that has been studied, the net effect is that as oxygen debt rises there is a progessive and exponential increase in the probability of death as a function of the increase in oxygen debt. This was suggested initially by studies of

Crowell and Smith (21), who examined the dose response curve for oxygen debt with regard to outcome and estimated that a 50% lethal dose (LD_{50}) occurred at 120 ml O_2 debt, per kilogram body weight. Using a quantitative model, Dunham, Siegel, Weireiter & Fabian, *et al.* (2), demonstrated that the LD_{50} occurred in 113.5 ml per kilogram body weight and showed that an accurate prediction of the probability of death (Pdeath) could be made for the magnitude of the oxygen debt curve. These studies showed that the Pdeath increased in expomential fashion as the oxygen debt rose (*Fig. 3*).

Recent experimental studies by Siegel *et al.* (3), have shown that either base deficit or lactate can be exploited to quantify oxygen debt and thereby to estimate the severity of the shock process from the previously demonstrated probability of death/O_2 debt relationship occurring both during hemorrhagic hypovolemic ischemia, as well as during the resuscitation from oxygen debt shock. This is shown in *Fig. 4* where a constant relationship between oxygen debt and lactate acid is demonstrated in an experimental model both during hemorrhage and during reperfusion.

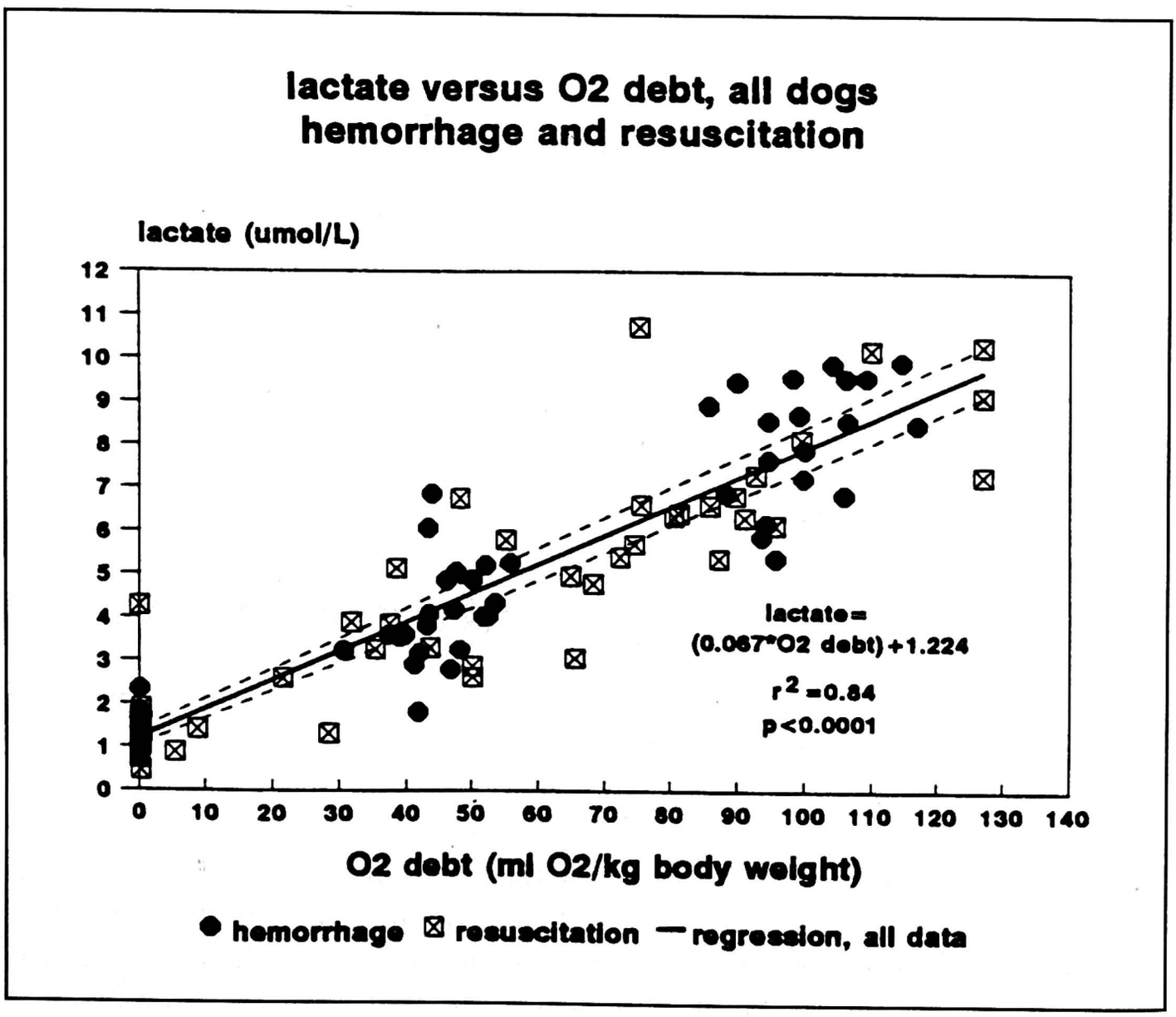

Fig. 4. Relationship of lactate to O_2 debt, canine data from Siegel, Fabian, Smith, Costantino (3).

Evidence for oxygen debt shock in man

These observations have been applied to man by Siegel, Rivkind, Dalal, *et al.* (22), to demonstrate that the initial arterial base deficit, or the initial blood lactic acid, can be fit to a linear logistic model to express the probability of death in patients following multiple trauma. Their study also showed that the interaction between oxygen debt due to hypovolemia in traumatic shock, as measured by its metabolic surrogate base deficit, is compounded by the presence of a closed head injury as indicated by the patient's admission Glasgow Coma Scale (GCS). Use of this model of the extracellular base deficit: GCS relationship enables a prediction of mortality to be employed as an index of severity in post-trauma patients (*Fig. 5*). Since this study, other clinical studies by Bakker and Vincent (23) as well as those by Davis, *et al.* (24), and Rutherford and colleagues (25), have confirmed that the metabolic parameters of oxygen debt (lactate and base deficit) can be utilized to stratify the risk or mortality and to provide a guide to the adequency of volume resuscitation following a traumatic or hemorrhagic hypovolemic insult.

EARLY AND LATE INFLAMMATORY CONSEQUENCES OF OXYGEN DEBT SHOCK: ARDS: The Acute Respiratory Distress Syndrome

It has long been noted that severely traumatized patients and those with episodes of profound hypovolemic shock are at risk for a number of major and independently life-threatening complications of the shock process. Not only are the metabolic correlates of oxygen debt (lactate acid and base deficit) logistically correlated with an increased probability of mortality from the shock process, but they are also related by a linear logistic function to probability of development of the adult respiratory distress syndrome (ARDS). The initial studies of ARDS by Faist and Baue (26) demonstrated that there was an early and late form of ARDS. By examining not only the admission base deficit and lactate, but also the nadir of the oxygen debt response within the first twelve to twenty-four hours in 80 severely injured multiple trauma patients, Rixen and Siegel (1) were able to demonstrate that the maximum oxygen debt response was related to the probability of developing early posttrauma ARDS occurring within the first four days after injury.

The use of the initial 24 hour period after injury was related to the need for operative intervention to control the source of continuing hemorrhage due to laceration or rupture of a solid organ or due to a major vascular injury. This study showed that a base deficit which was $\geqslant -6.6$ mMol per liter or a maximum lactate acid of $\geqslant 5.1$ mMol per liter was associated with a probability of $\geqslant 0.4$ for the development of ARDS. More important, those

patients who developed ARDS related to this level of shock induced metabolic ischemia had a greater than 80% chance of dying of the subsequent ARDS process.

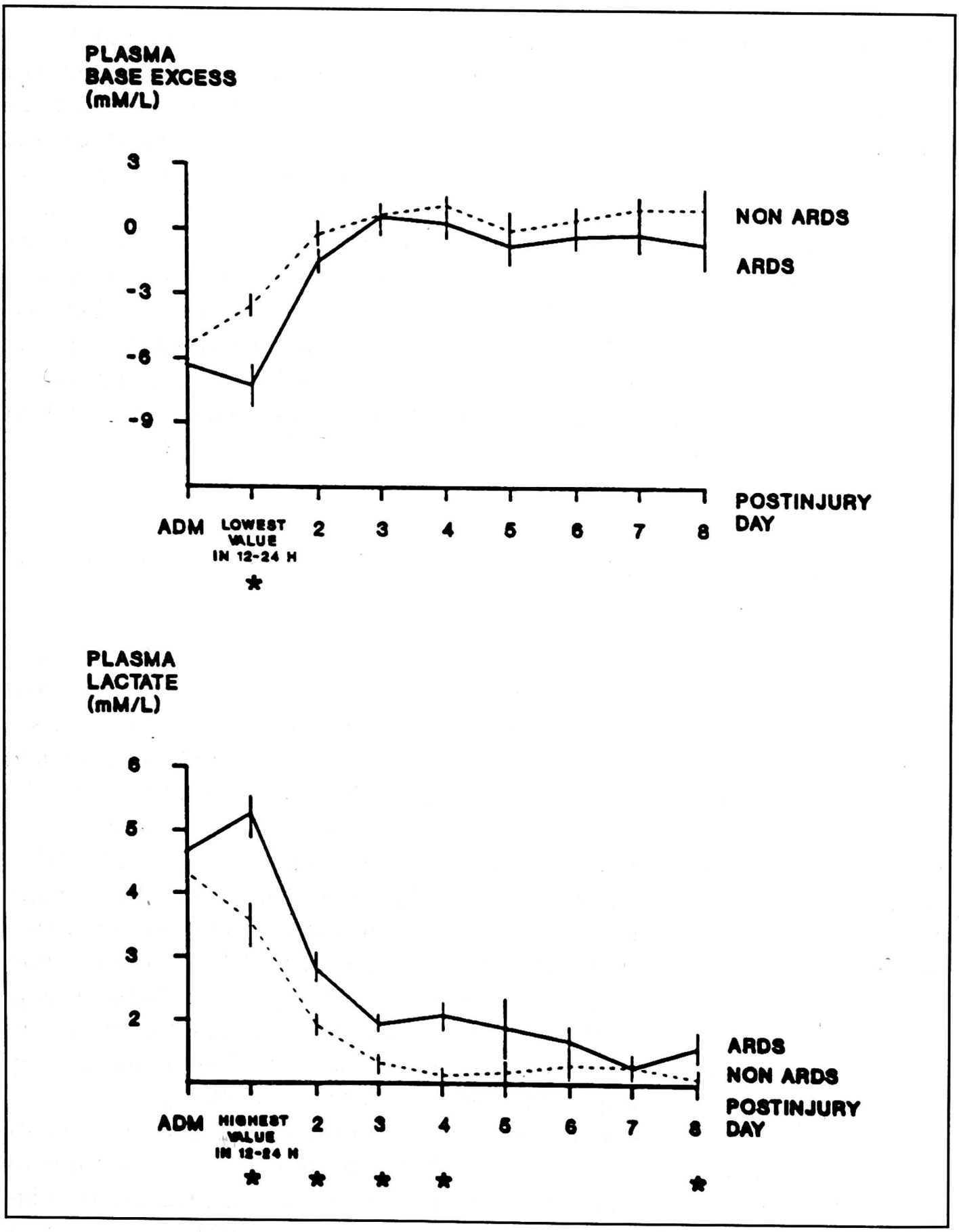

Fig. 5. Relation of post injury base excess and lactate to the development of ARDS. Data from 80 multiple trauma patients. From Rixen, Siegel (1).

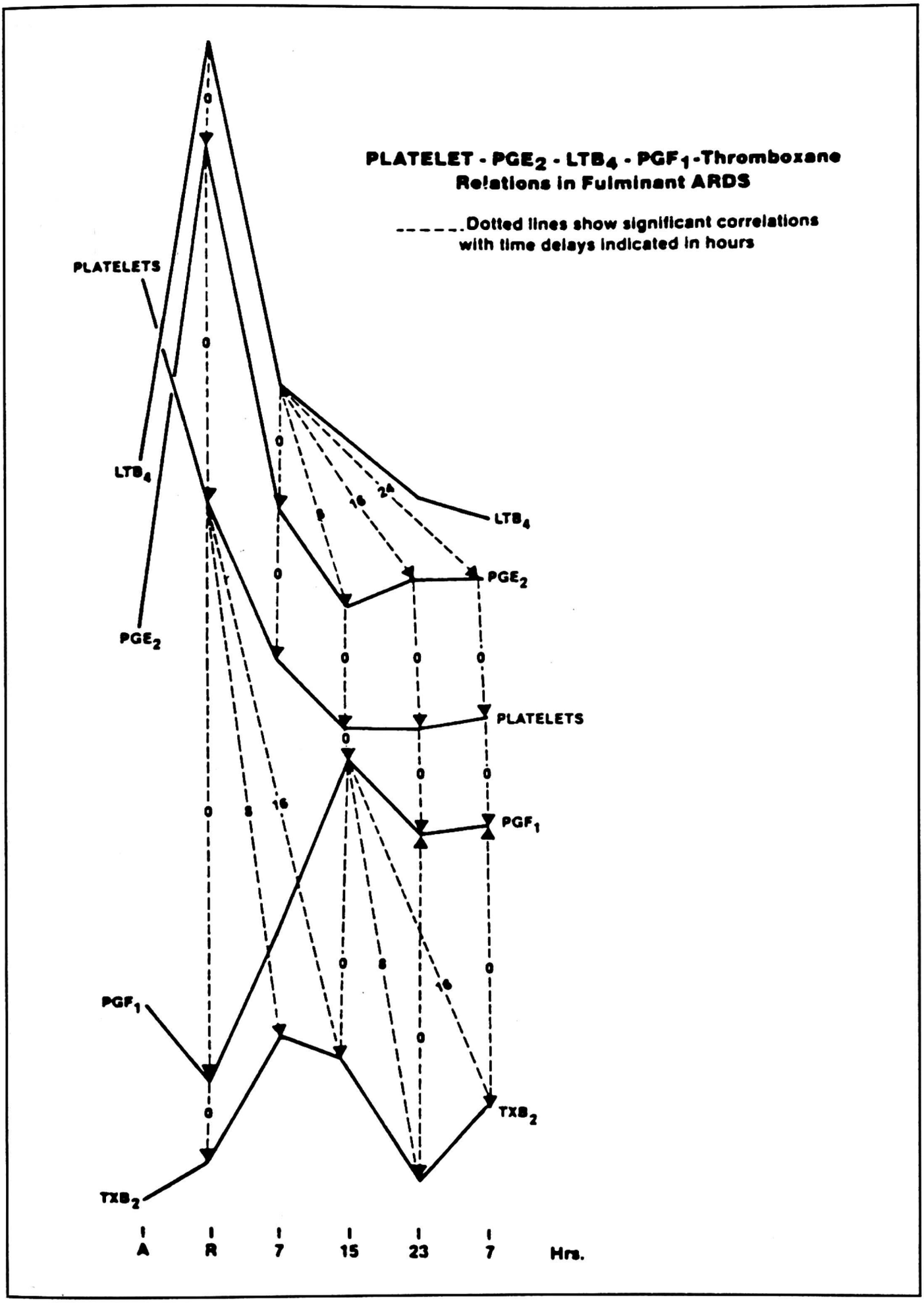

Fig. 6. Schematic of significant correlations between platelets, PGE_2, LTB_4, PGF_1, and TXB_2 in patients with fulminant ARDS. Taken from statistical probability data from Rivkind, Siegel, Guadalupi, Littleton (27).

The ischemia induced mediator response was quantified by Rivkind *et al.* (27) who demonstrated that the early fulminant form of ARDS was associated with an outpouring of large quantities of the eicosanoids LTB_4 and PGE_2 immediately after the establishment of reperfusion during the volume resuscitation period after hypovolemic shock. This was followed by the release of other eicosanoids most notably PGF_1 and thromboxane (TXB_2), as circulating platelets and leukocytes fall, suggesting platelet aggregation and adherence and leukosequestration (*Fig. 6*).

Early ARDS was associated with evidence of a rise in leukocyte myloperoxidase activity in the initial four days posttrauma with an increase in stimulated superoxide production measured by chemiluminescence levels which were significantly higher than those seen in the uncomplicated post-trauma response. The early ARDS superoxide levels were also higher than those seen in patients who did not develop ARDS early, but rather developed subsequent sepsis associated with late ARDS occurring after the initial four days post injury (*Fig. 7*) (28).

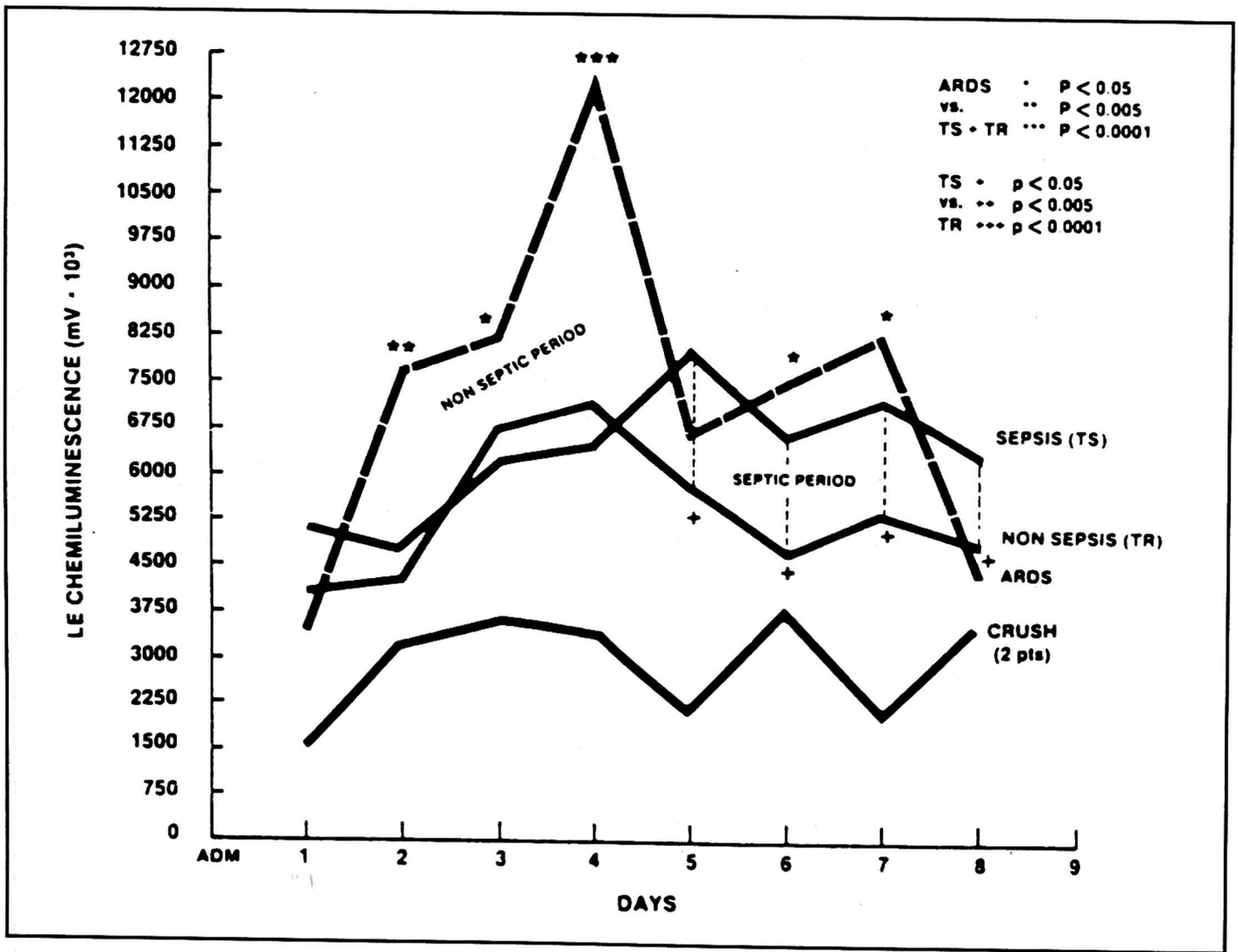

Fig. 7. Mean values for leukocyte chemiluminescence (patient cells in patient sera) in post-trauma ARDS, septic (TS), non-septic (TR), and crush patient groups. Each day's samples for ARDS, TS, and TR patients are considered as a three-group entity for simultaneous ANOVA determination of significance. Note significant increase in ARDS leukocyte chemiluminescence during early post-trauma period at days 2—4. From Rivkind, Siegel, Littleton, *et al.* (28).

Significantly, the rise in stimulated superoxide production was found in those post-trauma patients who had the greatest fall in circulating leukocytes, reflecting enhanced leukosequestration and presumed adherence to capillary endothelium (28). This suggests a direct relationship of a greater O_2 debt post-trauma to a subsequent more pronounced inflammatory response which characterizes the fulminant host defense response inducing early ARDS. In this regard, the studies of Rixen and Siegel (1) also demonstrated that the initial 12—24 hour mean base deficit achieved in the early ARDS patients was −9.4 mMol per liter vs −4.3 mMol per liter ($p < .05$) for those who developed late ARDS, and the corresponding values for lactate were at level of 6.4 mMol per liter for early ARDS vs 3.3 mMol per liter ($p < .05$) for those patients who developed late ARDS. Moreover, this increased level of ischemia parameters was related to an even greater probability (0.47) of developing ARDS and an increased probability of death due to ARDS (77%) in the early ARDS group, compared to only 50% in the late ARDS group and only 20% in the non-ARDS multiple trauma patients.

Of equal importance in their study was the relationship of the oxygen debt parameters (lactate and base deficit) to the subsequent cytokine response. These studies (1) showed that there was a greater subsequent mean IL-6 response in the first four post-injury days in patients who developed early ARDS (323 pg/ml) compared to those who developed a late ARDS response (141 pg/ml; $p < .05$), or compared to those who developed a non-ARDS IL-6 response (67 pg/ml; $p < .0001$). Similarly, the mean IL-8 level in post-injury days 1 thru 4 for patients with early ARDS (264 pg/ml) was significantly higher than that in the late ARDS group (68 pg/ml; $p < .05$). There were also increased IL-1 responses in early ARDS compared to non-ARDS, but no significant differences in the ARDS vs non-ARDS patients were seen in the tumor necrosis factor (TNF) responses.

These studies (1) also related the ischemia parameters and their related cytokine response to the aspects of the acute phase protein (APP) response which appears to be significant for the development and progression of the ARDS disease process. Since it has been demonstrated that IL-6 plays a direct effect in the simulation of the hepatocyte to produce fibrinogen (29), it would appear of interest that these studies (1) demonstrated that in the early ARDS patients, there was a significantly higher fibrinogen level than that found in the late ARDS patients and in those who did not develop ARDS. Fibrinogen is an important APP since it is related to coagulation properties that induce thrombosis in small vessels. Also because of the increased permeability in the area of vascular inflammation induced by the eicosanoid and cytokine responses, the increased levels of fibrogen result in the deposition of fibrin strands, especially in the lung. This fibrin deposition appears related to subsequent formation of immature collagen which in turn plays a role in the

late fibrosis and reduced lung compliance in this disease process (30). Thus the magnitude of oxygen debt seems to have important consequences in inducing most important pathologic expression of the initial phase of the host defense response disease process, early fulminant ARDS.

OXYGEN DEBT SHOCK AS A FACTOR IN THE INITIATION OF SEPSIS

A variety of experimental studies carried out by Rush *et al.* (31) as well as by Deitch and his colleagues (32), have suggested that hypovolemic shock may lead to an altered integrity of the intestinal mucosal barrier. These investigators demonstrated slughing of intestinal villi associated with an increased translocation of intestinal bacteria and bacterial endotoxin into the gut interstitial tissue and lymph nodes. There is also evidence that the post-trauma and septic vascular permeability changes also result in an increased leukocyte leukocyte infiltration into the gut interstitium and the liver. Moreover, experimental studies in chronic endotoxin infusion (33) and in an intra-abdominal septic abscess (Spolarics, work in progress, 1997) model have shown that the macrophage population of the liver is also increased in both of these conditions. Thus, there is evidence that the liver as well as the gut may function as an inflammatory organ under these circumstances and this change in state appears confirmed further by our studies which show increased cytokine production emanating from these same visceral organs under similar conditions in a chronic intra-abdominal abscess model.

Whether bacterial translocation is a mechanism by which septic processes are initiated in man following episodes of profound shock has not been clearly identified, although a number of suggestive studies have been performed. However, there is no question but that patients with the lowest base deficit and highest lactate levels following injury also appear to have the greatest probability of the development of sepsis (1, 22). Unfortunately for a clear scientific proof of this relationship in man, the evolution of the septic process after trauma is influenced by a number of important factors in addition to the functional level of the host defense response and the balance between the inflammatory and immune suppressant components of the human response as initiated by the traumatic episode. The propensity for sepsis development after injury is also influenced by the magnitude of dead and damaged tissue produced by the insult itself, as well as by the introduction of bacteria into the wound either by contamination with extracorporeal bacteria containing material, such as might be introduced from the outside by roadaide dirt, or by a penetrating missile. Bacterial invasion may also be effected by the penetration of a hollow viscus (colon or small bowel) containing large quantities of endogenous bacteria by a missile, or as a consequence of visceral bursting

trauma due to a seat belt injury. Also, the nature and virulence of the organisms introduced into the post-trauma injured tissues, their antibiotic sensitivity spectrum, and the local conditions for their growth in the wound also play a major role. All of these factors are difficult to quantify in terms of their relative influence in man. Nevertheless, the data strongly suggest that under any given set of circumstances the magnitude of the shock induced oxygen debt will influence the likelihood of the development of the septic process by altering the capacity for an effective host defense.

QUANTIFICATION OF THE HUMAN RESPONSE TO INJURY AND SEPSIS

Regardless of the mechanism of introduction of infectious organisms into the human body, it is important to gain quantitative knowledge concerning the level of adequacy, or inadequacy, of the human host defense response to this uncontrolled process. To achieve a measure of the adequacy of the human response a variety of schemes based on the examination of one or more variables obtained from sick, septic patients have been utilized as a means of quantifying the nature and severity of the septic process. These have been utilized as a means of quantifying the nature and severity of the septic process. These have included cardiovascular variables, variabless which reflect the level of metabolic acidosis (such as lactate nd base deficit), variables derived from renal function (such as creatinine clearance and BUN), variables developed from the utilization of various metabolic substrates, or those reflecting increased gluconeogenesis.

In many cases the values derived from these variables have been heuristically applied, such as in the Stoner-Elbute Sepsis Score (34), or in the broader based APACHE II scoring system (35). These logistically heuristic indices have been useful, but have been demonstrated to lack precision and to be poorly suited for the quantification of the human septic response, largely because they are not data-dependent and do not allow qualitative discrimination between critical aspects of the host's adaptive response, or permit precise quantitative severity stratification of the patient's compensation to the septic process. The more recent attempts (36) to define the systemic inflammatory response (SIRS) and to differentiate this inflammatory state from that seen in patients who develop the so-called "Sepsis Syndrome" have also tended to group together different aspects of the septic process in a manner which prevents discrimination between severities of septic illnesses, as well as the obscuring the different patterns of these disease processes.

To remedy this problem an attempt has been made to develop a physiologic classification system which also permits severity stratification. This Physiologic State Severity Classification System (PSSC) (37, 38) designed for Intensive Care

Unit Patients is based on the evaluation of seventeen simultaneously obtained physiologic variables, these include cardiac index (CI), heart rate (HR), mean arterial blood pressure (MAP), oxygen consumption index (VO_2/M^2), mixed venous pH (pHv), arterial base excess (BEA), mixed venous CO_2 tension ($PvCO_2$), total peripheral resistance (TPR), cardiac mixing time (TM) which is the wash-out from the ventricle of a cardiogreen dye bolus, cardiac vascular dispersive mean transit time (TD) which measures the time constant for transfer across the lung also developed from the cardiogreen dye curve, systolic ejection time (ET), right atrial pressure (RAP), Respiratory Index (RI) which is the alveolar-arterial oxygen gradient normalized by the PaO_2, pulmonary shunt (QS/QT), arterial CO_2 tension $PaCO_2$, arterio-venous oxygen content difference ($Ca\text{-}vO_2$), and the mixed venous oxygen tension (PvO_2). Each of these variables is normalized by the mean and standard deviation of the same variable obtained in a control group of recovering (R) trauma patients, which then converts the individual variables into a common scale of standard deviations from the reference control state (R STATE). By utilizing a clustering algorithm (K-means procedure) in the metric created by the above mentioned normalization, data-dependant groupings that manifest distinct physiologic patterns were developed (38). These prototype states have been consistently recovered from progressively larger groups of septic and non-septic post-trauma patient data sets. This process suggested seven consistent prototype physiologic states different from the R STATE of trauma recovery: A STATE of normal stress response, B STATE of metabolic insufficiency, C_1 STATE of early respiratory insufficiency, C_2 STATE of late respiratory insufficiency, D STATE of cardiogenic decompensation, and an H STATE of hypovolemia without shock. *Fig. 8* illustrates these seven physiologic state patterns.

Considered as an entity, each state prototype center has a unique mathematical distance and direction from the control R STATE in a multidimensional hyperspace. The R STATE classification prototype is placed at zero in all vectors in this multidimensional hyperspace by a normalization procedure. As a result, the seventeen-dimentional coordinates of each state center can be projected into a three-dimensional plot as shown in *Fig. 9* where the control prototype R STATE lies at 0,0, and 0 on the X, Y, and Z dimensions and all directions are scaled linear combinations of the seventeen physiologic variables in units of R STATE deviations. This projection allows the physician to visualize the quantitative physiologic pattern of the patient's host defense response and provides the ability to see the status of an individual patient at any given time in the clinical course relative to all the State centers. Thus two critical aspects can be characterized, the patient's response at a given time (which is a point in this hyperspace) can be classificed by quantifying the patient's distances to each prototype state (R, A, B, C_2, D, etc.) and the patient is then assigned to a Class by virtue of the closest State distance, this can be

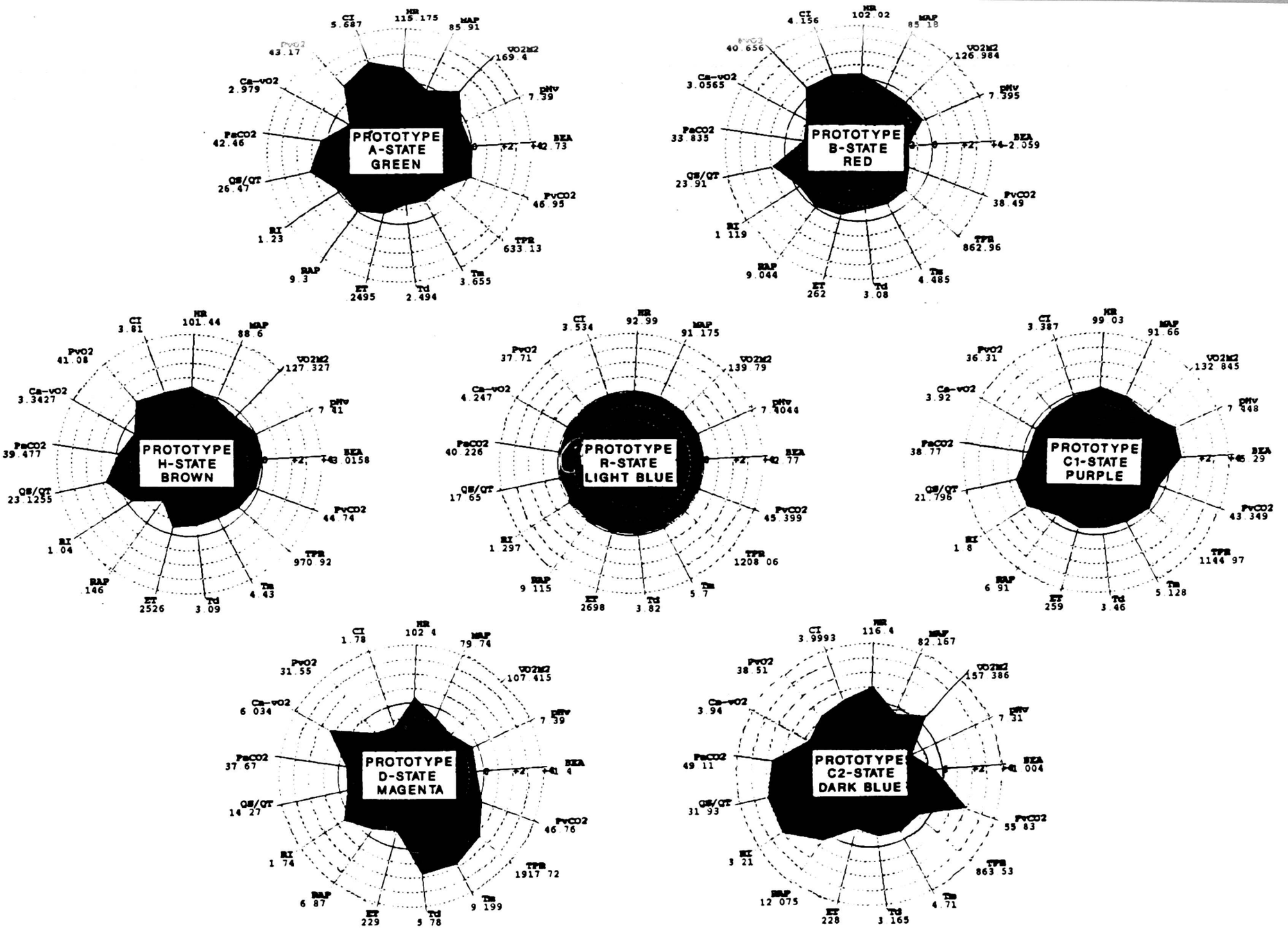

Fig. 8. Prototypes of physiologic states. All values are shown scaled by the means and their standard deviation of the respective values found in the R-State (reference) recovering trauma patients. The R-State means are shown at zero standard deviation and each dotted circle represents one standard deviation increased or decreased from the R-State means. Each State is expressed by an individual color. Computerized production of a colored circle diagram pattern enables the clinician to recognize the calculated physiologic state (circle diagram pattern and color) and to understand the physiologic response (pattern recognition) of an individual patient at a given moment of time. From Rixen, Siegel, Friedman (38).

seen in *Fig. 9* where the new patient was initially classified as an A STATE because of being closest to the A STATE prototype and then as he deteriorated he moves to a new location (heavy line) and is now classified as a C_2 STATE by virtue of his relationship at that moment in time to the C_2 STATE prototype mean value.

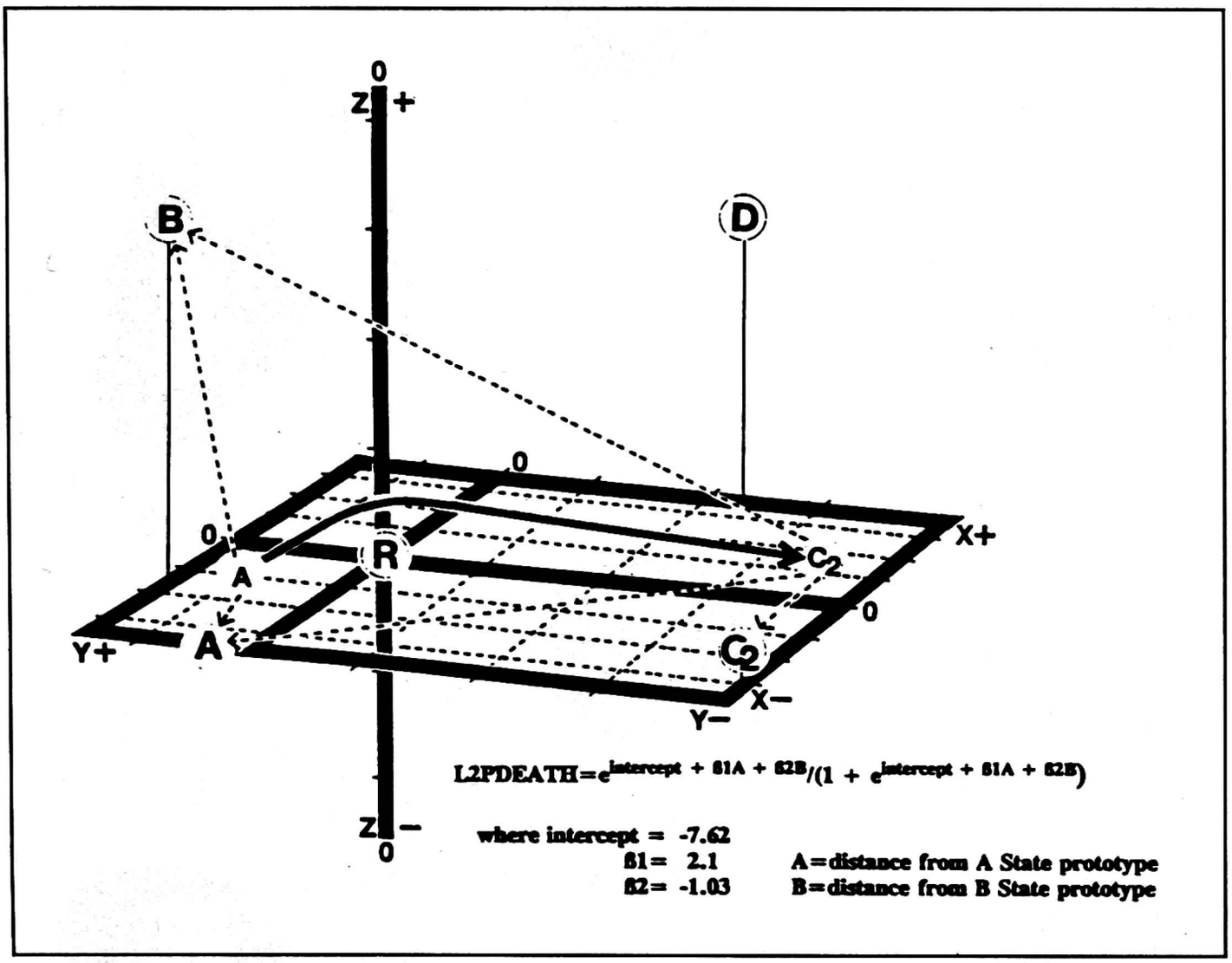

Fig. 9. Diagram of Physiologic State Space with prototype State centers identified. Time course of new patient from A-State to C_1State is shown, as is computation of probability of death (L_2Pdeath) with the appropriate exponent coefficients. From work of Siegel, Friedman, Rixen (37).

The second important piece of information which can be derived from this data transformation is that one can obtain precise stratification of the patient's illness severity at any given moment in time based on the specific State distances. To determine this a logistic model was developed using a developmental set of trauma patients and was then applied to a test set of new trauma patients not in the original data set. As shown in *Fig. 9* it was demonstrated that for the developmental set of trauma patients, the two major distance of which are of critical importance are the patient's distance at a given moment of time from the reference A STATE of a normal stress response and the patient's distance at the same moment in time from the B STATE of

metabolic insufficiency. It is observed from *Fig. 9* that patients with a C_2 STATE response characteristic of ARDS are also very far from the A STATE prototype center. This model was used to estimate the risk of death, measured by the probability of death and from this model a severity index (L_2 Pdeath) can be computed from the coefficients in the exponent of the patient's distance to the A and B STATES which have been determined by the patients values for the seventeen scaled physiologic measurements shown in *Fig. 8*. The logistic equation for the calculations of the L_2 Pdeath severity index for trauma patients is also shown in *Fig. 9*.

Fig. 10 is a projection of the three-dimensional physiologic coordinate system shown *Fig. 9* with the R, A, B, C_2 and D State prototype centers indicated. In this figure, the solid line box represents the mean $\pm$ one standard deviation of the last study of survivors before transfer from the ICU, while the interrupted line box represents the mean $\pm$ one standard deviation of the last study of non-survivors just before death. Projected on this space are 514 studies of a new group of trauma patients not in the original developmental model. These points are studies done at any time during their clinical course. The survivors are designated as "balloons" and the deaths as "pyramid" symbols. It can be seen that the patients who failed to survive lay for mist of their clinical course in regions of this space which were distant from that occupied by the studies from the group of survivors. The non-survivors tended to range rowards the C_2 and B directions, with the final studies of this group having very large A STATE distances.

Receiver-operator curves (ROC) for the predicitive index L_2 PDEATH showed that the optimal threshold was 0.5 with a highest true positive rate 0.83 at the low false positive rate of 0.02, which contrasted with the ROC curve for the APACHE predictive index of survival in that the APACHE-derived index (ARDEATH) was maximized at 0.759 at the low false positive rate of 0.02 with a probability of threshold of only 0.3, in other words only a 30% guess at non-survival (38). This indicates that the APACHE II index tends to under-predict death and thus the severity of patient's condition may be under-treated because it will not be correctly assessed. Moreover, this blurring of severity stratification, by both APACHE II scoring and the "Sepsis Syndrome" designations, makes stratification prior to randomization for therapeutic trials a virtual impossibility and has undoubtedly contributed to the difficulty in assessment of a variety of new and experimental measures in large scale clinical trials (37).

The Physiologic State Classification (PSSC) (37, 38) is also an indicator of the post-trauma mediator response. Of equal value in this classification system, is the ability of this utilize this physiologic state space to delineate the magnitude of the cytokine (39), histamine (40) and the nitric oxide (41) mediator (*Fig. 11*) responses. The distribution of plasma values to this latter

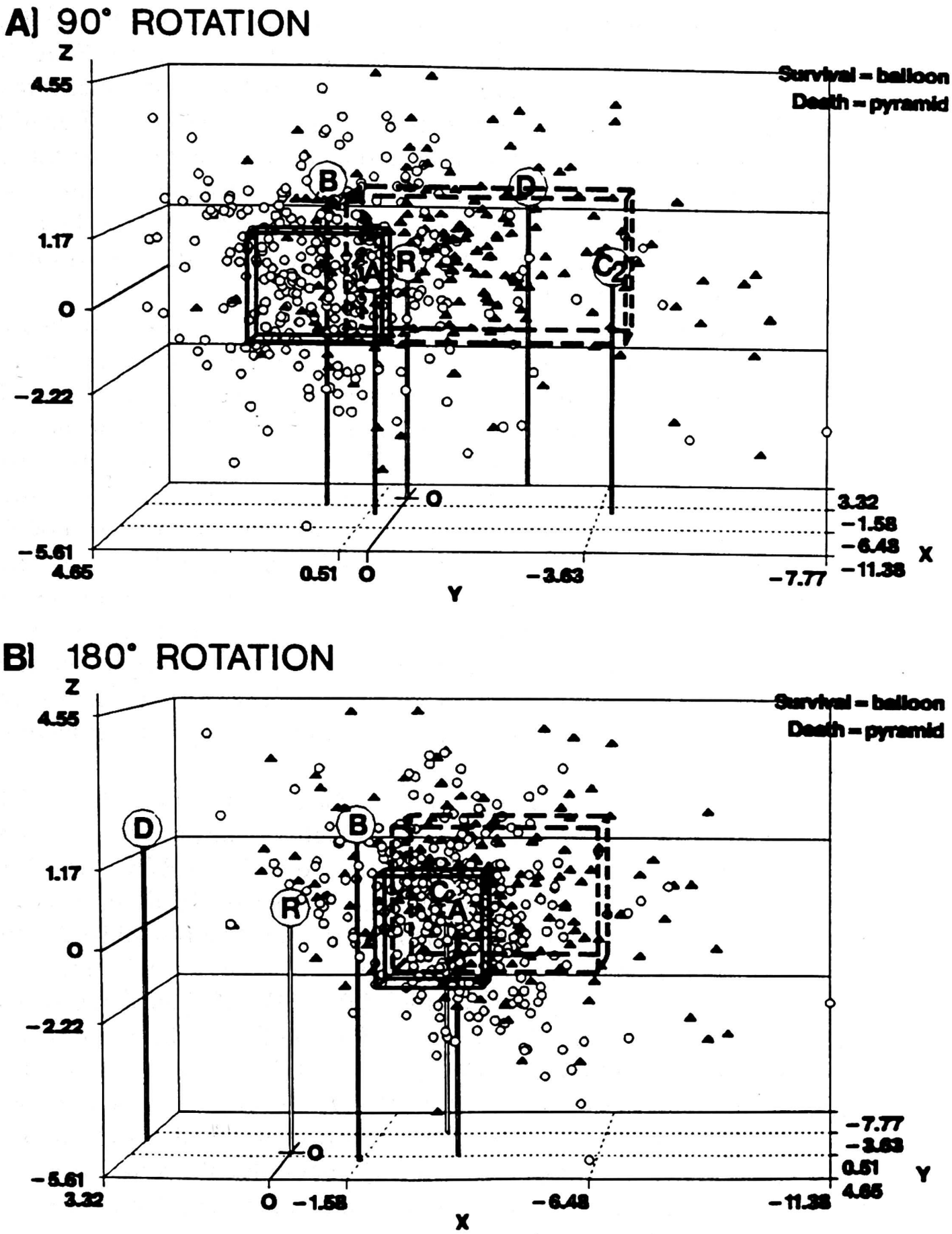

Fig. 10. Scatter Plot of 514 studies from 80 multiple trauma patients in 3 dimensional Physiologic State Space. *Fig. 10A* is a rotation of *Fig. 9* to 90 degrees to show the best separation of survivors (balloons) from deaths (pyramids) in the A—C_2 distance dimension, whereas *Fig. 10B* is a rotation to 180 degrees to show the best separation in the A—B distance dimension.

Solid box is ± 1 standard deviation of survivors
Dotted line box is ± 1 standard deviation of deaths
All studies over the entire ICU course are shown
Studies from survivors are shown as balloons
Studies from deaths are shown as pyramids
From Rixen, Siegel, Friedman (38)

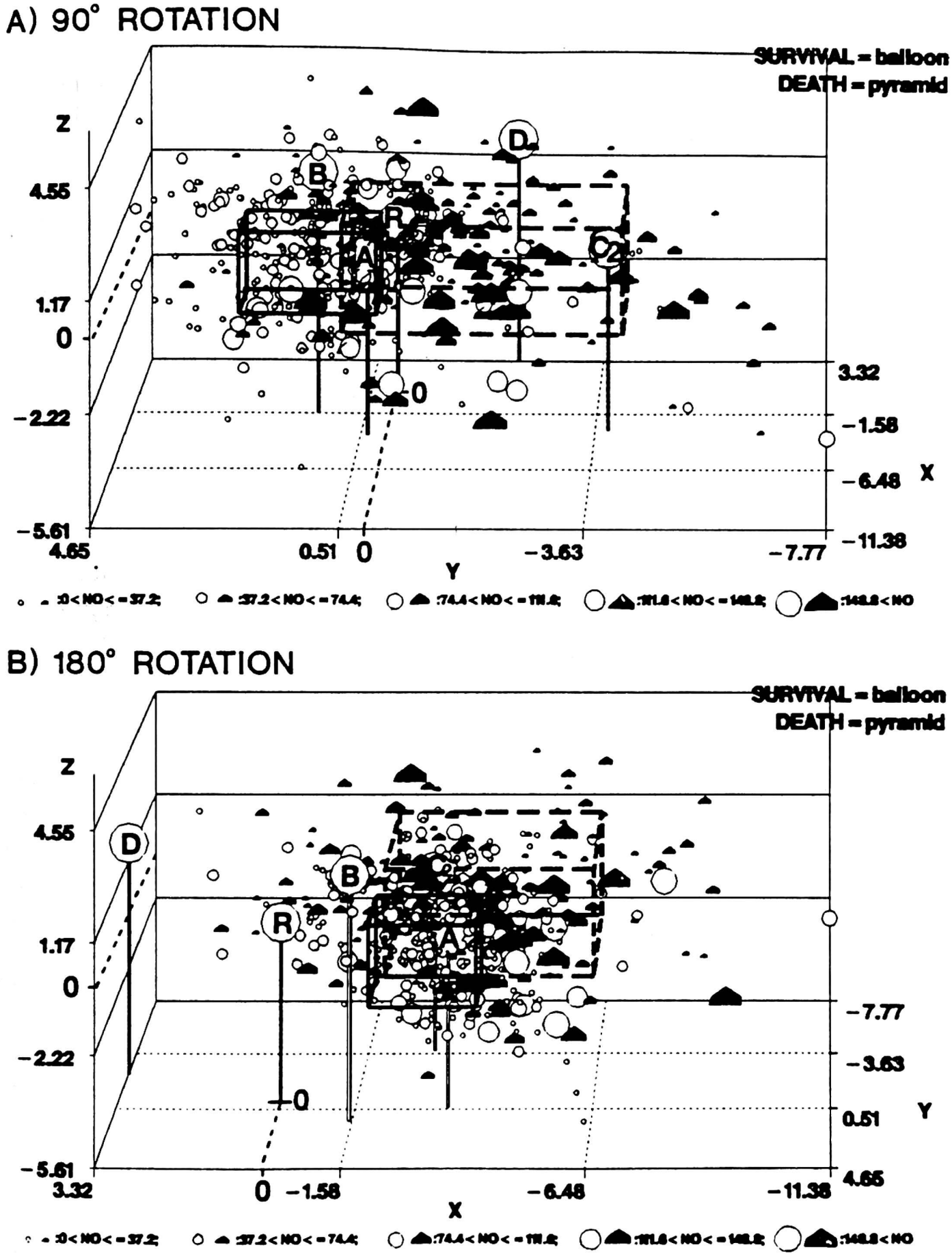

Fig. 11. Scatter plot of 514 studies from 80 multiple trauma patients in the same 3-dimensional coordinate system as shown in *Fig. 10*. *Fig. 11A* is a rotation of *Fig. 9* to 90 degrees to show the best separation of survivors (balloons) from deaths (pyramids) in the A–C_2 distance dimension, whereas *Fig. 11B* is a rotation to 180 degrees to show the best separation in the A–B distance dimension. NO ($NO_3 + NO_2$) scale in five ranges from smallest to largest balloon or pyramid. Ascending from $0 < NO \leqslant 37.2$, $37.2 < NO \leqslant 74.4$, $74.4 < noo \leqslant 111.6$, $111.6 < NO \leqslant 148.8$, $148.8 < NO$ (in μmol/l). Legend as in Figure 10. From Rixen, Siegel, Espina, Bertolini (41).

mediator is shown in a slightly rotated projection of the same physiologic space shown earlier in *Fig. 10*. In this projection, it can be seen that when the patients shown in the previous figure who had the most severe clinical non-survival characteristica, they also tended to have the highest values of nitric oxide. At these same time periods, these patients were also found to have the highest values of inflammatory cytokines most notably IL-6, IL-8, and to a lesser extent IL-1 (39). Moreover, those C_2 and B STATE patients who had high plasma values of these inflammatory mediators but who survived (large balloons in *Fig. 11*) tended to return to low levels of NO and inflammatory cytokines (small balloons in *Fig. 11*) as they moved closer to the A STATE prototype (*Fig. 10* and *11*).

DISCUSSION

There are two concepts, which have evolved from the studies summarized in this body of work. The first is that the initiation of the host defense response in a previously normal healthy host following a major traumatic episode appears related to the magnitude and extent of the oxygen debt produced by hypoperfusion (11, 12). This may occur in a localized area of tissue mass producing a focal inflammatory response, or in the case of severe trauma where there is a shock episode which reduces perfusion sufficiently to produce a generalized oxygen debt, the inflammatory response becomes systemic. After an oxygen debt, tissue reperfusion activates the interrelated cascade of superoxide, eicosanoid, cytokine, and nitric oxide responses (11, 12). The magnitude of the shock induced oxygen debt is directly related to the probability of death and this likelihood can be estimated, in both animals and man, from the shock levels of the metabolic correlates of ischemia anoxia (lactic acid and the extracellular base deficit) (2, 22). Moreover, the magnitude of the initial oxygen debt, reflected in these metabolic variables, can be also related to the likelihood that the patient will develop an early pathophysiologic inflammatory response manifested initially in the pulmonary vasculature, producing the fulminant early acute respiratory distress syndrome (ARDS) (1).

The second concept is that anoxic stresses of moderate degree that are well compensated initiate an adaptive host defense that in turn induces a hyperdynamic normal stress response, which can be characterized by the pattern of metabolic and physiologic variable values and by the shock mediators released (8, 38, 43). By the use of multivariable analysis of the patient's physiologic data at a given movement in the clinical course, the adaptive state of the patient's host defense can be quantified. Patients who develop a pathophysiologic transition into various forms of sepsis or the adult

respiratory distress syndrome (ARDS) have a different pattern of physiologic and metabolic variables which can be quantitatively defined (38—43).

Considered together, these differing physiologic and metabolic patterns represent distinct physiologic states which can be characterized by techniques of multidimensional data analysis. As a patient improves or worsens, the patient undergoes movement within a Physiologic State Space. Consequently, at any given moment in the clinical course, a specific critically ill patient has a precise pattern of physiologic as well as mediator and hormonal metabolic adaptive responses. The adequacy of the patient's host defense response can be measured by analysis of these selected physiologic variables and given the values of these variables at any given time, the patient can be mathematically represented by a single point (vector) in a multidimensional coordinate system. This point is the patient's Physiologic State and the totality of all patient points, or vectors within this space is denoted as a Physiologic State Space (38). Changes in the patient's Physiologic State are reflected in the values of his or her physiologic and metabolic variables. The patient's current State and change in State can be evaluated by comparing the patient's present pathophysiologic values to those of a control set of studies obtained from an historical data bank which enables specific locations within this State space to be identified as representing various types of pathophysiologic adaptation.

The evolution of the post-trauma patients injury status from a normal stress response into either an early fulminant ARDS, or into a state of metabolic decompensation characteristic of sepsis in which interorgan fuel: energy shifts occur driven by the eicosanoid and cytokine mediator complex, can be characterized by the patient's location within the State space, which is different for each type of host defense adaptation (1). The concept of Physiologic State helps to reduce the dimensionality of the physiologic and metabolic response to trauma and sepsis. The patient's location within the State space not only reflects his physiologic and metabolic pattern of host defense adaptation, but also has implications with regard to the severity of the disease processes. Thus the patient cannot obly be classified with regard to the characteristics of his host defense response, but also can be stratified with regard to the severity of illness.

The A STATE prototype represents the mean location of patients with a normal stress response to trauma or sepsis. Patients who tend to do well, tend to group in this area and to maintain an A STATE response throughout their clinical course until recovery occurs. The B STATE center is the mean response location of patients who have a multi-variable pattern characteristic of the metabolic failure which occurs in severe non-respiratory sepsis. These patients are characterized by substrate utilization failures, most notably excessive gluconeogenesis and lipogenesis associated with extensive muscle proteolysis (42) and an abnormal hepatic acute phase protein reprioritization (44). In

contrast the C_2 STATE center is the main response location of patients who manifest a predominant respiratory failure often associated with post-trauma ARDS, or with acute septic pneumonitis. The D STATE center represents the physiologic and metabolic adaptations seen in severe cardiogenic failure and after acute myocardial infarction.

Since patients may move between states, they may also maintain a location at any vector point within the Physiologic Space. Consequently, the metabolic and respiratory failures associated with the different multiple organ disfunction syndromes can be characterized both with regard to the nature of the disease process as well as with regard to its severity. Movement from one point in the Physiologic State Space to another, presents as a changing vector in this multi-dimensional coordinate system. This movement can be quantitatively determined and improvement or deterioration of the patient's clinical condition can be estimated with some degree of quantitative security. Most importantly, the Physiologic States Space developed from analysis of cardiovascular and metabolic variables also contains information regarding the underlying pattern of mediator responses, with the probability of high levels of cytokines (39), histamines (40) and nitric oxide (41) mediators being most commonly found in patients with B&C_2 State deteriorations. However, the highest nitric oxide levels are found in patients with pulmonary sepsis who manifest a C_2 Physiologic response pattern (4).

The philosophic conjecture, with respect to preventing patient deterioration into an excessive early non septic inflammatory response and its subsequent progression into a severe septic, metabolic or respiratory insufficiency state, is that attention must be paid to the development of a hypovolemic ischemic oxygen debt after injury. Given the present state of our knowledge, the quantification of this process by virtue of the easily obtained metabolic correlates of oxygen debt (lactic acid and base deficit) in the first few minutes and hours following injury and/or shock and their use as a guide to resuscitative therapy with appropriate volume restitution and perfusion enhancing therapeutic agents is more likely to abort the subsequent mediator driven pathophysiologic host defense responses than is later therapy directed at blunting an excessive inflammatory eicosanoids and cytokine release, or therapy directed at inducing a modification of an altered immune suppressive mechanisms induced by PGE_2 or anti-inflammatory cytokines.

Finally, clinical trials of effective therapeutic agents for an established septic response in man require proper classification of the nature of the septic response, as well as a pretreatment stratification of the host defense response with regard to severity (37, 38). Unless this can be done in a fashion contemporaneous with the selection for randomization and prior to the administration of the test therapeutic agent to be compared with best standard therapy, it will not be possible to ensure that both the control and the

therapeutic groups are equivalent. In this regard the utilization of techniques of multi-variable analysis to quantify the posttruma injury and septic patterns, would appear to have great value in assessing therapeutic outcomes in clinical trials.

Thus, injury and sepsis initiate complex humoral and cellular inflammatory responses that initially effect the microvascular system, but rapidly extend to involve and modulate the solid organ metabolic response (4, 12). The complex interaction between these cellular processes and the organs which they involve appear to be initiated by the trauma induced oxygen debt. The resulting host defense response requires classification by type and quantification of severity. These can be accomplished by the utilization of techniques of multi-dimensional analysis (38) which conceive of the patient's adaptive response as reflecting movement within a Physiologic State Space in which the adequacy of the physiologic pattern and metabolic processes determine the location and direction of change.

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