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Identifying and Understanding Patterns and Processes in Human Shock and Trauma

Abstract: The aim of this paper is to provide an overview of an on-going collaborative effort of research physicians, computer scientists, and statisticians to develop a quantitative way of understanding the clinical course of a critically ill and injured patient. The method is based on a multivariable analysis of time series of individual physiologic measurements. The ultimate goal is to reduce a large body of complex physiologic data to an information base that is relatively small and simple so that abnormal patterns may be exposed in a manner that can be directly interpreted and utilized at the bedside by the attending clinician to improve patient care. In this paper we describe some contributions made toward reaching this goal.

Introduction

Medical and social progress have increased the expectancy of life by sustaining many who would have succumbed in an earlier age to congenital or acquired diseases. This progress has increased the number of aged and other younger, but high-risk, patients who require major surgical procedures for the correction or palliation of their disease processes. It has also increased the magnitude of the medically abnormal population who are at risk from accidental injury or intentional trauma. In contrast to younger or physiologically more normal individuals, these patients frequently manifest more than one pathologic process, mainly degenerative diseases and neoplasms. Nearly all have some degree of arteriosclerosis—even if this is not clinically diagnosed—and many have associated chronic cardiac, renal, hepatic, or pulmonary disease. Anemia and low-grade subacute infections of urinary tract, bowel, and lung are also common. Because of these factors and others they constitute a group at higher risk from any trauma, be it surgical or accidental.

In such patients, it becomes critical that the surgeon have available some technique of physiologic assessment to classify the patient's present state and progress. The work of several groups of investigators [1–9] has suggested that an individual patient's ability to survive an acute stress is a product of the complex interaction among the functional adequacy of the mechanisms for myocardial, peripheral vascular, and pulmonary compensation.

The aim of this paper is to describe a quantitative way of understanding the clinical course of a critically ill and injured patient based on the multivariable analysis of the time series of individual physiologic measurements. By expanding the concept of obtaining a physiologic state classification to accommodate both a more comprehensive view of organ and system dysfunction, and to encompass change and the direction of change over time, we believe we can develop earlier predictors of crisis situations than currently exist.

We wish to define a parametric quantification of functional organ interactions (cardiopulmonary and cardiovascular) in terms of a measurement set that can be conveniently monitored on a continuous or frequent intermittent basis. Our objective is to analyze the data in order to utilize fewer and less destructive measurements for the on-going assessment of patients. This requires evaluation of various clinical measurements with regard to their ability to give early indications of significant pathophysiologic change.

Ultimately, we wish to use our analytic techniques to reduce the dimensionality of the complex physiologic data to relatively simple information that summarizes and exposes the abnormal patterns. The results will be presented in a manner that can be directly interpreted and utilized at the bedside by the attending clinician to improve patient care in the different areas of trauma as modified by intercurrent disease.

In this paper we describe some of the contributions that have been made toward this ultimate goal. In our view the most significant aspect of our work has been the establishment of a multivariate frame of reference within which one can begin to interpret human physiologic data from the desperately sick. This frame of reference has permitted the identification of physiologic patterns that can help the physician make decisions concerning the care and treatment of critically ill patients.

Multivariable state classification in human shock

In order to develop our classification techniques, a computer data bank of patient information was established from cases arising from the surgical services of a large metropolitan hospital. This data bank currently contains clinical, cardiovascular, metabolic, and therapeutic data on 245 patients. The data originate from sources including bedside cardiac catheterizations, patient records, laboratory determinations, and physicians' and nurses' notes. The patients were studied over a time period ranging from less than one day to nearly one month; the number of detailed studies on individual patients ranged from 1 to 62. Each study consisted of a set of measurements centered on a determination of cardiac output. In some cases up to 151 primary variables of the type indicated above were involved and up to 61 additional derived variables were produced. The present data bank of 245 patients contains 1485 such measurement sets. The data are cross-sectional with regard to the measurement sets of all patients and longitudinal with regard to many sets on an individual patient. This is diagrammed in Fig. 1, in which the clinical histories of two variables for two patients are plotted. The various measurements on an individual patient at a point in time are keyed to the determination of cardiac output with a dye dilution method. The physician's clinical description of his patient may change from one time period to another. In addition to the digital type of data indicated above, analog recordings of the dye dilution measurement performed at the bedside are available.

Figure 2 shows dye curves for two patients with myocardial infarction shock and indicates that the curves may have very different shapes even though the levels of cardiac output are essentially identical, i.e., the areas under the curves are nearly equal. Our previous clinical and experimental work has demonstrated that a dye curve can be described by a functional mathematical model with serial components of delay, dispersion, and mixing [10]. This model quantifies the magnitude and shape of the dye curve in terms of four independent parameters. One of these, the flow, is inversely proportional to the area under the dye curve, and the three others are the delay (TA), the mixing mean transit time (TM), and the dispersive mean transit time (TD) across the cardiac-pulmonary circuit. On the basis of experimental and

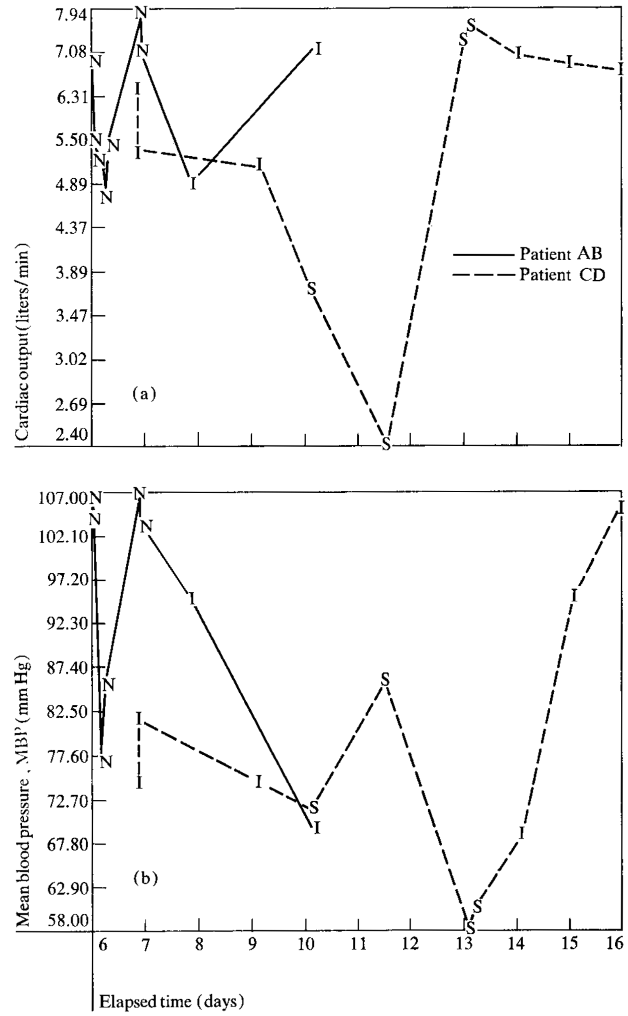
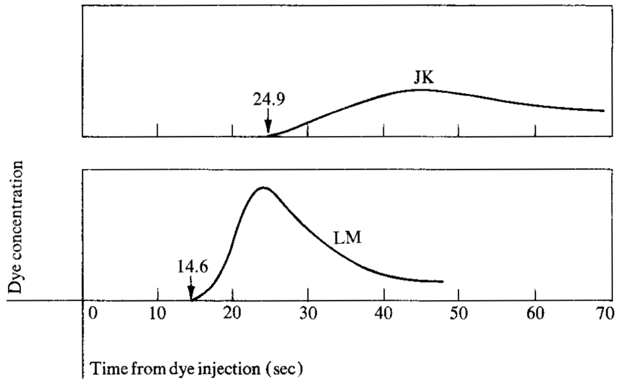


Figure 1 Clinical condition histories of two patients. (a) Cardiac output; (b) mean blood pressure. The notations N, I, and S refer to the clinical conditions "Control," "Infection," and "Infection plus Shock," respectively. In this and following Figures, fictitious initials are used to identify patients. (After Fig. 1 [12].)

clinical studies, we developed a physiologic interpretation for the parameters. Delay is primarily related to passage through the large vessels. Mixing time (TM) is related to the durational aspects of left ventricular pressure development [11]. Thus, it is a correlate of the maximum velocity of contractile element activity and hence reflects changes in ventricular contractility [5,7,10,11]. Experimental data suggest that dispersive time (TD) usually indicates the mean transit time through the small vessels of the pulmonary vascular bed [10]. However, an excessive prolongation of TD can often indicate a significant area of myocardium that has no intrinsic contractile activity [10,11].

Clinical, physiologic, and mathematical judgment provided the basis for choosing the following physiologic variables for detailed analysis: the cardiac index (CI),



Patient	*Cardiac output (liters/min)*	*Appearance time (sec)*	*Dispersive time (sec)*	*Mixing time (sec)*
JK	1.54	24.9	13.31	43.3
LM	1.79	14.6	5.24	10.6

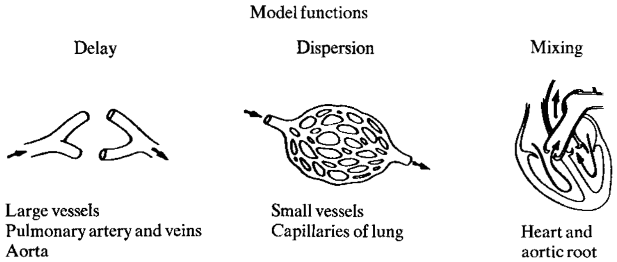


Figure 2 Dye curves and model parameters from two patients with acute myocardial infarction shock. These patients had not been aided with mechanical support therapy prior to the time these data were obtained. (After Fig. 2 [5].)

the mean blood pressure (MBP), the arterial-venous oxygen content difference (AVDIF), the heart rate (HR), the cardiac ejection time (ET), the central venous pressure (CVP), the mixing mean transit time (TM), and the dispersive time (TD). (The cardiac index is the cardiac output normalized by dividing by the patient's body surface area. The cardiac ejection time is the time during the heart beat that the aortic valve is open and blood is ejected from the heart.) A logarithmic transformation of these variables was used, since various linear combinations of the logarithms of these primary variables have a direct physiologic interpretation. The additional physiological variables, venous pH (VPH), venous pO_2 (VPO2), and venous pCO_2 (VPCO2) were also included, making a set of eleven variables containing information concerning the state of the heart and of the peripheral circulation. (pO_2 and pCO_2 are the partial pressures of oxygen and carbon dioxide, respectively. The pH is the negative log of the hydrogen ion concentration.)

In this discussion, "samples" are thus vectors of these eleven physiologic measurements taken simultaneously on a patient at a discrete moment in time and may be considered as points in an eleven-dimensional space. Just as the physician may consider his patient to be in different clinical "states" at different times in his clinical course, the assumption was made that a patient's measurement sets may reflect different physiologic "states." Therefore, it seemed reasonable to analyze all patient sample sets independently of their relationship in real time. We thus assumed that the totality of the patient samples describes the range of pathophysiologic states. Also, we thus did not explicitly treat the covariance structure within an individual patient's set. All samples from patients who had evidence of cirrhotic liver disease were deleted from the analysis since this entity has physiologic features similar to a variety of septic states and therefore blurs classification of septics. It is also a rather complicated chronic condition with other prominent features that permit its clinical diagnosis on the basis of other measurements.

An initial step was to seek to establish a way of looking at the data in this eleven-dimensional space that the physician could relate to his knowledge and information on these patients as stored in the computer. In this study it was possible to define a "basal," or reference, set of samples on purely clinical grounds. This was done by deleting from the analysis samples from patients who had acute myocardial infarction (MI) and samples taken from patients under anesthesia, obtained during infection, or when there was clinical evidence of septic or nonseptic shock. The remaining patients had an age spread and range of chronic disease processes similar to the septic and MI group, but were not acutely ill. The idea behind the analytic approach was to view the possible different patterns of physiologic adaptation in the septic and other shock samples as being departures from the "basal" group of similar high-risk patient samples. It was both desirable and necessary to refer the measurements to a control group derived from the patients under study, since this group is the clinical population from whom all the patient sets arise and the measurements used are not routinely performed on healthy individuals. A healthy person, even of the same age and sex, is as different from these high-risk patients as is an elderly patient from a young person.

After the initial clinical selection of the basal group, all of the samples were re-examined solely in terms of the quantitative measurements to be sure that they formed a reasonably homogeneous group from a quantitative as well as a clinical point of view. The means and standard deviations of this purified basal group were used as the normalizing factors for the entire population. Data-inferred groupings of patient samples were selected by means of a categorizing procedure referred to, in general, as cluster analysis.

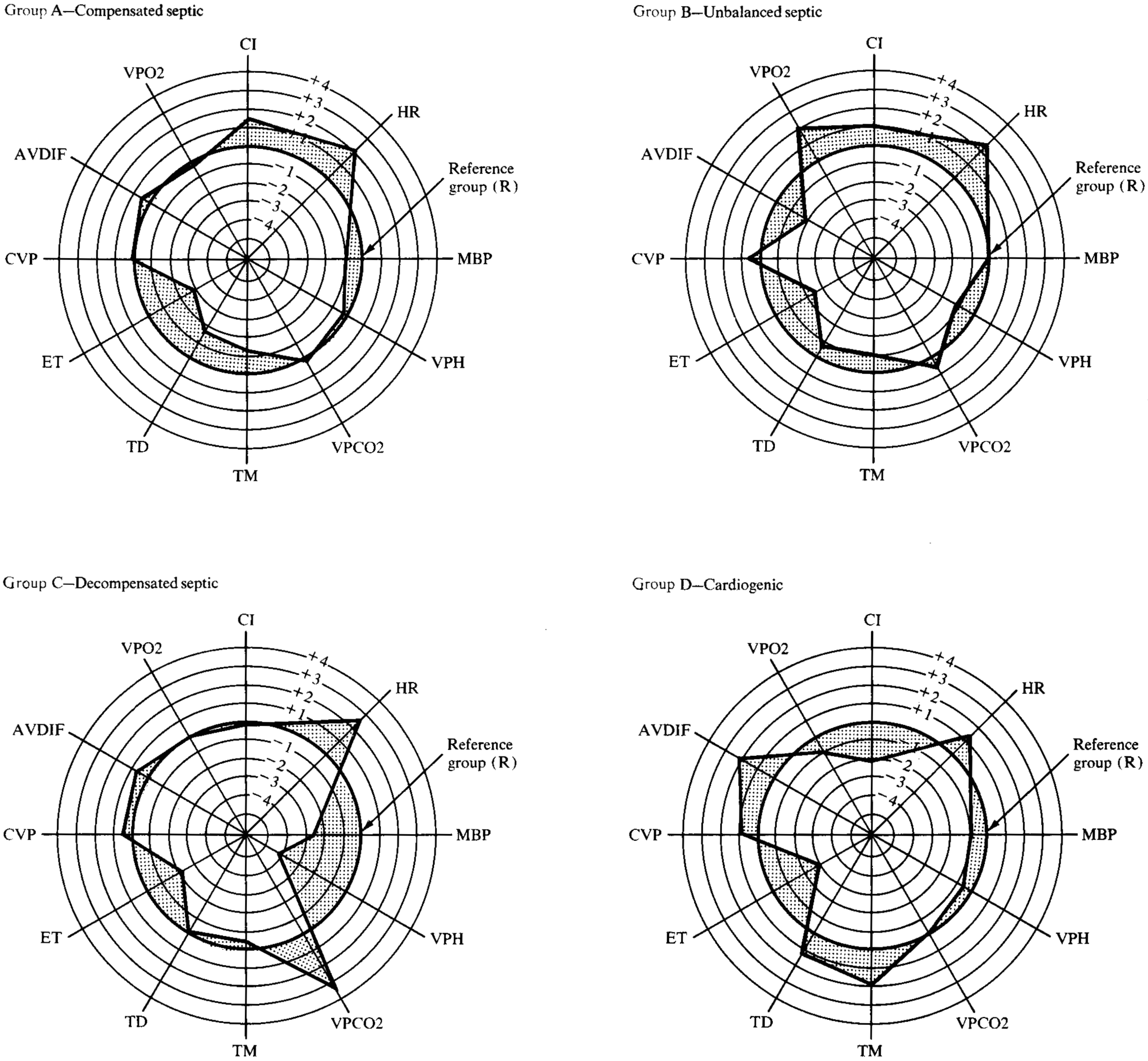


Figure 3 Physiologic patterns in the multivariable means of the four cardiogenic and septic groups: A, B, C, and D. The numerals on the concentric circles are the numbers of standard deviations from the mean of the reference group R. (After Fig. 6 [5].)

The present methodology of "cluster analysis" (i.e., the procedures for arriving at data-inferred categories) covers a broad area of loosely related techniques, objectives, and concepts. One cannot point to a "blueprint" or master plan from which one goes from data to a set of categories. Rather, algorithms and criteria for grouping data must be concatenated with other techniques of exploratory data analysis, and the results evaluated and interpreted within the context of the subject matter under study. The statistical criteria used in the present context are described in [12]. The data analytic methods used to derive the results described in the discussion that follows are documented in [13].

These clustering procedures led to the definition of four pathophysiologic groups, and a fifth group composed primarily of basal patients (labeled R state). Three of the pathophysiologic groups contained the entire spectrum of clinical severity in sepsis [4]. These groups are labeled in alphabetic order, A, B, and C. The septic states show patterns in the means of the eleven variables that represent prototype patients with increasing physiologic imbalance and worsening prognosis. For patients who

Table 1 Mean values of physiologic variables and number of standard deviations (in parenthesis) of the normalized values from the corresponding mean of the R group. A level of ±1.90 standard deviations is used as the minimum level for consideration as a physiologically significant difference between means. (After Table 1 of [5].)

Patient state and number of patients in each state	*Mean values of physiological variables**										
	CI ($l/min/m^2$)	MBP (mmHg)	AVDIF (Vol. %)	HR (beat/min)	ET (sec)	CVP (mmHg)	VPH (pH)	VPO2 (mmHg)	VPCO2 (mmHg)	TM (sec)	TD (sec)
	Normalizing factor										
	0.127	0.0986	0.159	0.0730	0.0565	0.486	0.0762	10.38	9.34	0.179	0.126
R	2.54	88	3.7	78	0.30	2.7	7.43	39	39	4.3	4.8
185	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0)	(0.0
A	3.91	73	4.2	115	0.21	2.8	7.42	35	39	2.6	3.0
252	(1.48)	(−0.80)	(0.36)	(2.33)	(−2.77)	(0.05)	(−0.12)	(−0.36)	(0.01)	(−1.23)	(−1.58)
B	3.58	81	1.7	114	0.21	4.9	7.35	60	44	3.0	3.6
118	(1.18)	(−0.36)	(−2.03)	(2.29)	(−2.52)	(0.53)	(−1.00)	(1.98)	(0.57)	(−0.88)	(−1.01)
C	2.45	51	4.5	115	0.19	5.5	7.10	40	70	3.7	4.4
37	(−0.11)	(−2.36)	(0.56)	(2.32)	(−3.52)	(0.63)	(−4.27)	(0.13)	(3.31)	(−0.36)	(−0.33)
D	1.32	72	7.3	99	0.20	6.5	7.39	26	40	10.5	7.0
103	(−2.21)	(−0.87)	(1.88)	(1.42)	(−2.89)	(0.79)	(−0.52)	(−1.25)	0.12	(2.15)	(1.28)

*Except for the variables VPH, VPO2, and VPCO2, the mean values shown are the antilogarithms of the mean of the log values, and the normalizing factors represent ±1 standard deviation from the log value of the corresponding mean of R.

enter the C state, death usually occurs within 12 hours unless they are reverted to an R, A, or B state.

The fourth group (D state) is found to be primarily composed of multivariable samples from patients with acute myocardial infarction [5,11]. A few sample sets in the D group came from patients without MI's who had severe hypovolemic shock. A small number of data sets came from septic patients studied after open-chest cardiac massage, or during cardiac failure. There were also a few samples in the D group from aged pre-operative patients who had neither acute MI nor shock. These patients all had a compensated low flow state because of severe chronic coronary artery disease with extensive myocardial fibrosis. In several cases there was a documented chronic left ventricular aneurism. As in the most decompensated septic shock state (C), a large number of the samples found in the cardiogenic group D came from patients who succumbed from their acute disease process within 24 hours of the data collection period. Of the 31 patients whose last recorded study was in the D group, 22 died. These data indicate the severity of prognostic information about the abnormal physiologic pattern reflected by the D-state multivariable set [5,10,11].

A summary of the physiologic pattern exhibited in each of these states as compared with the reference group (R) is shown in Fig. 3. This figure shows the departure of each variable from that of the reference group in standard deviations of the means, and reflects the quantitative distortion pattern of a prototype patient for each abnormal group (A, B, C, D). Table 1 shows the numerical values from which these patterns were plotted.

Interaction of state classifications and model parameters

Two major aspects of this study were done in parallel. The results of the cluster analysis and modeling tended to reinforce and lend credibility to each other. This phenomenon is described in the sequel. The vital role of the computer in performing the study is discussed in Ref. 14.

The initial results with clustering were based on a set of nine variables that excluded LTM and LTD inasmuch as the parallel work on functional physiologic modeling of indicator dilution had not yet been completed. This cluster analysis yielded the five groupings we have referred to as R, A, B, C, and D. The behavior of the nine variables used to define the clusters was quite similar to that of the eleven-variable clustering given in Table 1.

A parallel effort in the development of a functional physiological model for indicator dilution has partially been discussed in an earlier section of this paper. A physiologic interpretation of some of these parameters has also been given and is indicated in the lower part of Fig. 2. Reference has been made to the fact that the mixing time TM is correlated with ventricular contractile function. This fact has been documented in other works in which it was shown in an individual subject that there is a strong correlation between TM and the durational correlate of ventricular contractile activity [5,10,11].

Applied to the clinical cases under study (Fig. 4), the mixing time also appears related to the adequacy of myocardial function in myocardial infarction. Over the

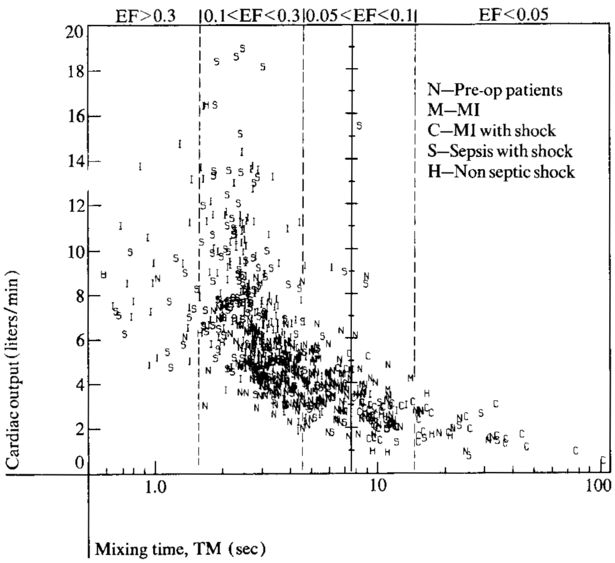


Figure 4 Cardiac output as a function of mixing time (TM) showing separation of MI patients from pre-operative control patients with respect to TM (line shown at TM = 7.5 seconds). Pre-operative patients with TM greater than 14.6 sec had chronic left-ventricular aneurysm. The dashed vertical lines separate ranges of ejection fraction (EF), which is the ratio of stroke volume to mixing volume. (After Fig. 3 [5].)

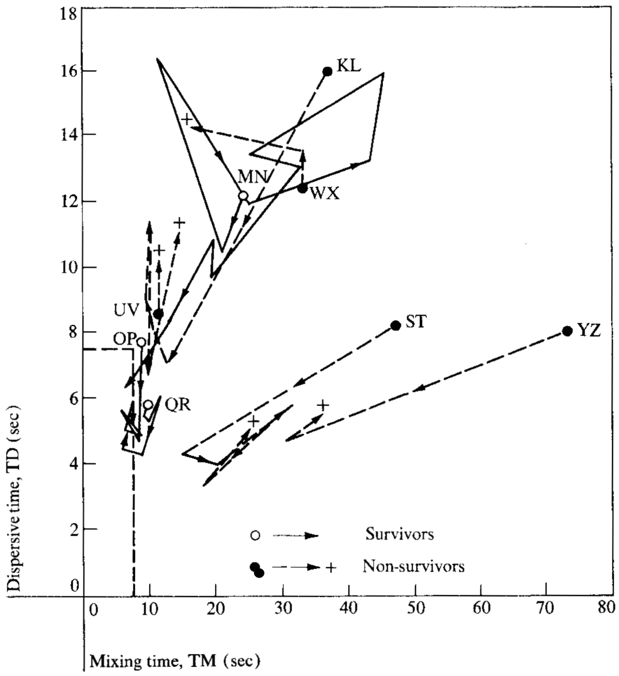


Figure 5 Trajectories in the TM-TD plane of eight patients with myocardial infarction who underwent intra-aortic balloon counterpulsation. The trajectories drawn as dashed lines indicate patients who died, while those drawn as solid lines identify the patients who survived. (After Fig. 4 [5].)

same range of flow, patients with acute myocardial infarcts (C and M) had marked prolongation of TM (greater than 7.5 sec) and reduced ejection fraction (EF) compared to control pre-operative patients (N), or patients with hypovolemic shock (H) uncomplicated by cardiac failure. (EF is the ratio of stroke volume to mixing volume.) Conversely, the patients with high flow septic states (S and I) had a lower TM and increased EF; the exceptions in the septic group being patients with clinical high output failure, or those septic shock patients who were studied after a cardiac arrest.

The relationship between TM and TD is a guide to the effectiveness of mechanical support therapy in the patient with an acute infarct. Figure 5 shows the trajectories of 8 of the 9 patients who underwent intra-aortic balloon counterpulsation (IAB) using the Bregman-Goetz dual-chambered catheter assist device [15]. The three patients who were resuscitated from acute MI shock by this technique had both the TM and TD reduced below the critical level of 7.5 seconds. The six nonsurviving patients had transient improvement, but were not able to achieve a sustained reduction in TM and TD. Of 28 MI patients studied to date, no patient in whom TM and TD values both remained above the 7.5 second level has survived the acute episode in spite of medical inotropic therapy or mechanical support (IAB).

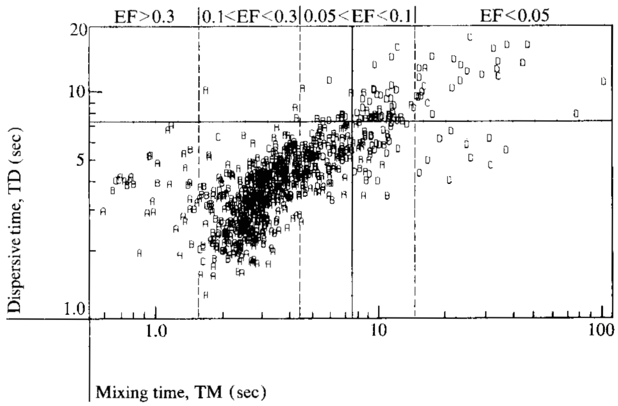


Figure 6 Dispersive time TD as a function of mixing time TM, showing the relation between these parameters of the dye curve model and the original nine-variable physiologic states, R, A, B, C, and D. The TM-TD plane is divided into quadrants by lines drawn at the critical 7.5-sec times on the axes. (After Fig. 5 [5].)

The results at this point seem to indicate that the group identified as D contains the majority of those patients who had suffered from myocardial infarction and who have poor cardiac function. There was some evidence that the parameters in the modeling, TM and TD, contained direct information regarding this contractile

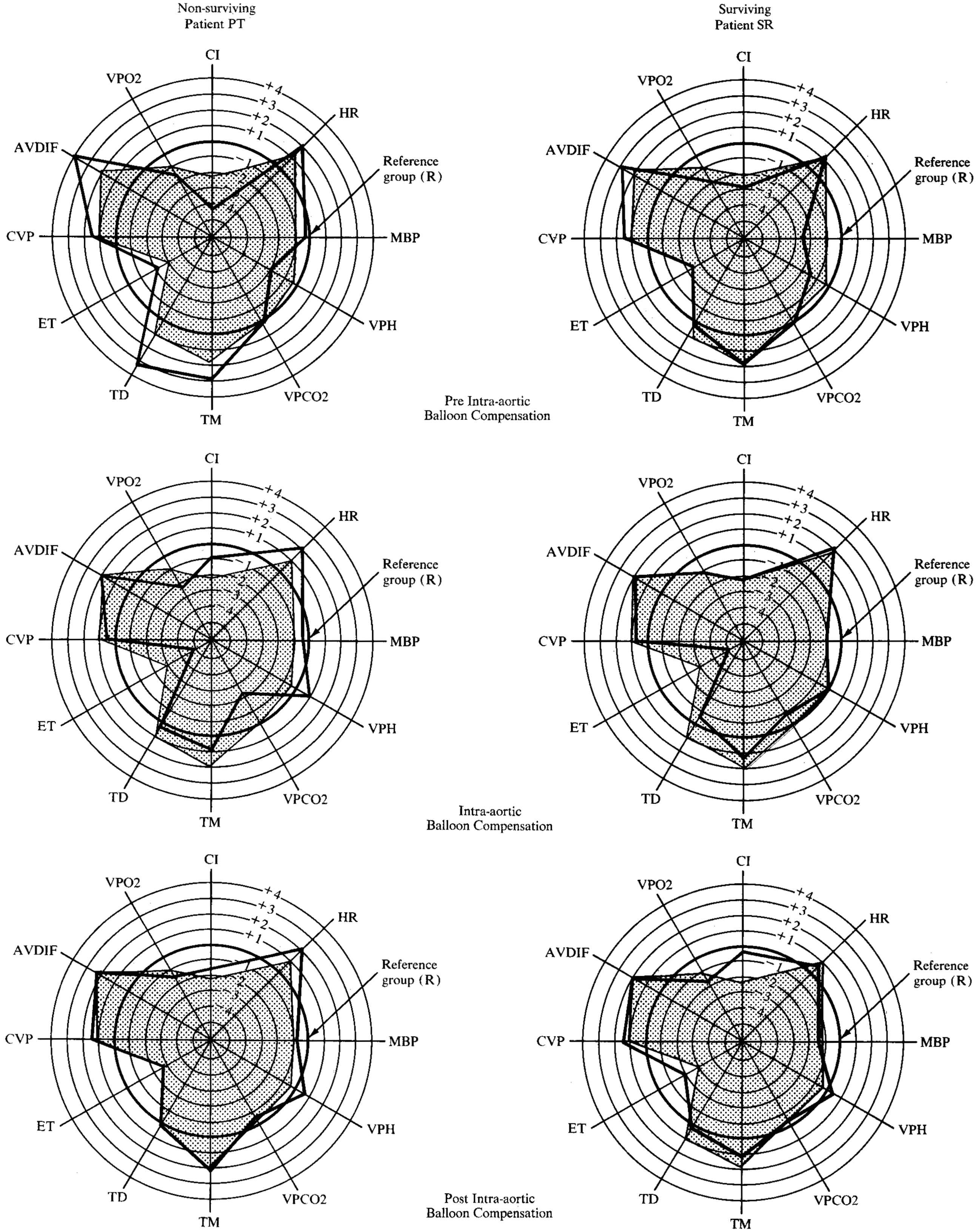


Figure 7 Multivariable patterns plotted from data taken at three times in the clinical courses of surviving and nonsurviving MI patients treated with IAB. The patterns describing the condition of patient PT who died, represent the first, ninth, and fifteenth studies of his condition. The patterns referring to patient SR, who survived, represent the second, seventh, and ninth studies. The shaded areas show the means of the prototype physiological state D. (After Fig. 9 [5].)

function. Hence, a very important consideration was to determine the correlation between this group D and the model parameters TM and TD. The result is perhaps best shown by reference to Figure 6. This figure shows TD versus TM with the individual samples labeled according to the cluster analysis states (R, A, B, C, D). It should be readily apparent in that figure that most of the D patients are in the upper right quadrant, which corresponds to poor ventricular contractility, as previously indicated.

Interpretation and clinical applications

The nature and direction of the deviations from the control condition (the R state) in the septic and cardiogenic shock patients support the contention that different mechanisms are involved [4,5,12]. The pattern of the means of the physiologic variables in severe sepsis and their usual progression with increasing severity from the compensated state (A), to the unbalanced state (B), into the decompensated septic shock state (C) suggest that the major factor is a peripheral lesion producing a major disparity between effective cellular perfusion and overall tissue blood flow. These data suggest that myocardial depression in sepsis, though an important and serious complication, is not a primary feature of the disease process. This assertion is supported by the prototype patterns shown in the A, B, and C circle diagrams (Fig. 3). From B to C there are progressive increases in venous acidosis (i.e., decreasing VPH), hypercarbia (VPCO2), and in oxygen extraction (AVDIF), and decreases in MBP that are disproportionate when compared to the lack of significant change in cardiac index (CI) or myocardial contractile function (TM). In contrast, as noted above, the severity of cardiogenic shock (D state) appears directly related to the degree of myocardial contractile depression (TM). The D circle diagram shows that the significant decrease in cardiac index (CI) and the increase in AVDIF appear roughly proportional to the prolongation in TM. The reduction of cardiac flow in MI shock seems to occur in a process where the important peripheral perfusion/flow disparity is not a major aspect, since widening in the AVDIF is approximately proportional to a reduction in flow. Note that neither the mean blood pressure drop nor the increase in venous acid production are significant discriminators of the group pattern, although they may be important features of a particular patient's illness.

It is clear that a given patient's response to his primary disease process evolves over time and that this evaluation takes place in a physiologic continuum. Probably no real patient is exactly like the prototype patient whose values represent the multivariable pattern of means needed to define the physiologic state. The prototype states provide a grid over the physiologic continuum so that the physician can interpret what is happening to his patient and make clinical decisions. Viewed in this light, the value of these physiologic parameters in clinical decision-making in myocardial infarction shock is shown in Fig. 7. This figure abstracts nodal points in the detailed time course of two patients with medically refractory cardiogenic shock who required intra-aortic balloon counterpulsation [5,15]. One survived after IAB and one died in spite of a period of support. However, the logical implications of the study of the time course of the changing physiologic patterns offer a guideline for more rational therapy based on the patient's physiologic state.

Both patients were studied initially at a time when their acute MI had produced a profound decrease in cardiac output that had not been reversed by inotropic or volume load therapy. Because of the poor clinical picture and the quantitatively abnormal physiologic pattern, mechanical support using the Bregman-Goetz dual-chamber intra-aortic assist device [15] was begun.

Although both patients remained in the D state during the two days of study, it is clear that in both patients there was physiologic improvement with IAB inasmuch as the reduction of TM and TD suggested better coronary circulation. In addition, a rise in VPH and a fall in VPCO2 and AVDIF, suggested an improvement in peripheral perfusion that was somewhat greater than might be expected from the small increase in the cardiac index. The ejection time was reduced during IAB, due probably to the systolic unloading. The response in patient SR after IAB was completed was a continued movement away from the prototype D pattern back to the R state represented by the reference circle. In the case of patient PT, on the other hand, the initial improvement during IAB was followed by progressive worsening of the total pattern—cardiac and peripheral (movement toward the D state prototype). The therapy applied to SR was able to reduce TM to less than 7.5 seconds and he survived. This was not the case with PT, who died.

Our studies suggest that patients with myocardial infarction have a different pattern of physiologic abnormalities than other shock patients, and that the functional severity of the primary cardiac lesion and the resultant peripheral response can be quantitatively defined in a frame of reference that relates the abnormal physiologic pattern to an expected norm. More important, by evaluating both the specific aspects of the abnormal pattern and the total picture defined by the pattern, a rational scheme of physiologically based clinical decision-making can be specified [5,16].

Three physiologic variables dominate in distinguishing the cardiogenic group (D) from groups having patterns of septic shock (A, B, C) and from the control group (R). These are the cardiac index (CI), the arte-

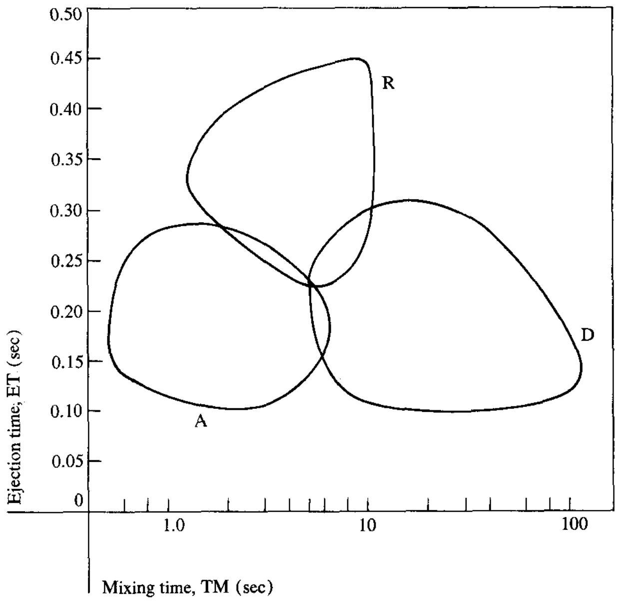


Figure 8 Ejection time versus mixing time.

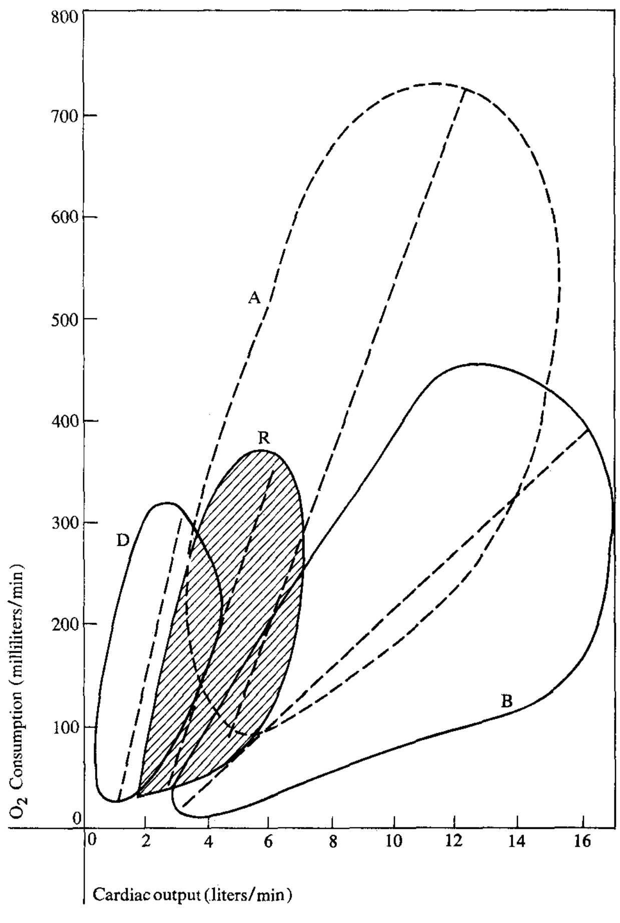


Figure 9 Oxygen consumption versus cardiac output flow. The straight lines represent the mean data trends.

riovenous O_2 gradient (AVDIF) and the myocardial contractile correlate (TM). The venous pH (VPH) also provides a major distinguishing variable separating the cardiogenic group (D) from the decompensated septic patients (C state). The ejection time (ET) is useful in differentiating the D-state patients from the control group, but not from other shock states. The dispersion component (TD) aids in differentiating D from the septic shock states. These observations follow from Fig. 3.

Additional studies were performed in an attempt to validate and understand the results obtained in the early studies. Figure 8 is a plot of ejection time versus TM. As can be seen, TM provides a good discrimination between groups A and D and ejection time has some effect in separating the R group from those with pathophysiologic defects. Physiologically, this suggests that the R group has a less dynamic myocardial function than the A-group patients, but is more dynamic than that of the D-state cardiogenic patients. This is explained by the force-velocity relationship of the myocardium. At a given myocardial contractile level with a lower after-load (i.e., peripheral vascular resistance), the velocity of shortening will be higher and the ejection time shorter.

Figure 9 is a plot of oxygen consumption versus cardiac output. Regions encompassing most of the A, B, D, and R groups are drawn in this figure. Oxygen consumption is the product of the cardiac output and the arteriovenous oxygen content difference (AVDIF). The breakup indicated is certainly consistent with the patterns as indicated in Table 1 and suggests a different pattern of peripheral oxygen consumption. The details of this cardiorespiratory interaction are described in [16].

Figure 10 shows a power (physiologic work) function versus TM and in this particular plot groups A, C, and D are outlined. Physiologically, this plot seems to suggest that a more dynamic contractile state (A group) is associated with a greater capacity for cardiac power than is the poor contractile state present in the D group. In contrast, C-state patients have poor power capacity, not because of uniformly decreased cardiac function, but because of severe peripheral abnormalities resulting in an abnormal pressure-flow relationship that causes a low blood pressure.

Our present feeling is that the basic set of eleven variables contains information about heart and peripheral activity, but is perhaps not as meaningful as we would desire in providing information about the respiratory function. As an initial study of respiratory regulation, pH and its relation to metabolic CO_2 production, arterial bicarbonate ion concentration is plotted as a function of arterial pH in Figure 11. It is physiologically interesting to note that the C-state patients previously shown to have abnormal work function because of low blood pressure are also the group with the greatest acidemia, which the plot shows to have both metabolic and respiratory components [16]. To quantify the cardiorespiratory interactions and to determine the clinical observability of these interactions, a detailed simulation of basic cardiogenic, respiratory, and metabolic functions was developed [17,18]. These simulation studies provide essential data for refinement of the eleven-variable set with respect to respiratory function.

Concluding observations

In conclusion, we review the progression of ideas related to the derivation of the results and make a few general observations. Our first analysis was based on an initial set of nine variables chosen because they give information about peripheral function felt to be important in the development of the shock state. Also, at that point in our studies [4,12,14] the myocardial patients were purposely excluded. Hence, our analysis was strictly limited to those patients with sepsis and septic shock, viewed in a framework derived from those patients who were basal. This approach was chosen to permit us to deal with a single pathologic entity. The C group appeared as a main effect in the data analysis at that particular point. The recognition of the prognostic implication of the C state resulted in earlier and more aggressive therapy in the antecedent B state, and as a result, fewer C-state patients were seen in the new cases as the study progressed. The very pathological patients who went into the C group were mainly those whose physiological records had been obtained over a four to five year period. Thus we feel the results we found were as much due to the careful step-by-step selection of the patient population as to the statistical methods of analysis. If one were to perform a similar analysis on the set of samples currently in the data bank, the effect of the relationship of the small number of C samples might be masked by the presence of large numbers of myocardial patients (non-septic).

We view the multivariable means derived from the various groups as a way of summarizing the data, and as a technique of imposing a grid or scale on the eleven-dimensional continuum. One can view the label—the derivation of the state—as being a very brief summary of the physiologic status of the patient. However, inasmuch as no patient lies precisely at the prototype mean of his particular group, it is necessary to understand motion in the eleven-dimensional physiologic space, and this is one of the questions that is now under investigation.

Another point worthy of mention is that without a physiologic grid on the continuum one is unable to ask a variety of very important questions. For example, without the definition of a B state, a C state and an A state out of the clinical condition of sepsis, it is impossible to ask whether different responses to therapeutic programs

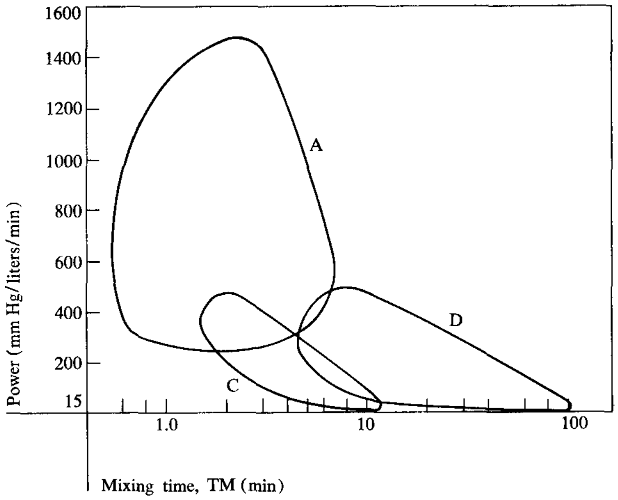


Figure 10 Physiologic power (mean blood pressure times cardiac output flow) versus mixing time.

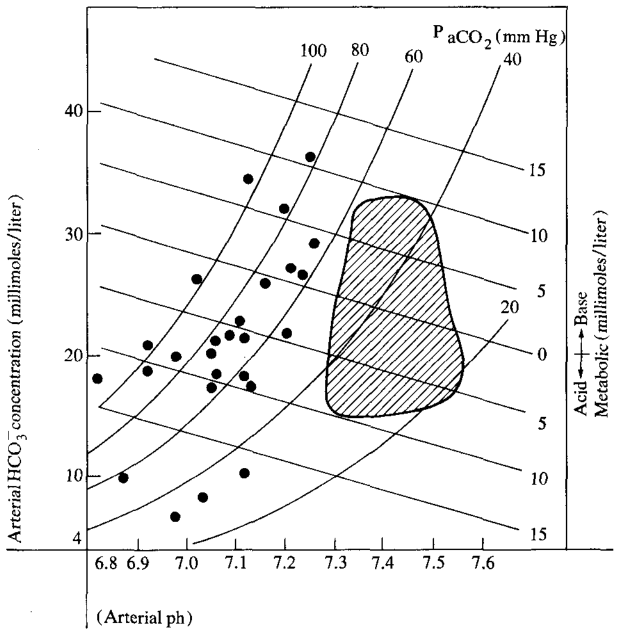


Figure 11 Bicarbonate ion concentration versus arterial pH. The dots represent C-state patients and the shaded area represents pre-operative patients.

are the result of different underlying patterns of compensation in a complex chain process. There is some physiologic evidence to support this contention and with the kind of framework outlined above, this is a reasonable type of question to attempt to answer.

An important consequence of this study has been the realization that, in attempting to work in a biomedical environment and to derive results that will be medically and therapeutically beneficial, it is important to have complete interaction between physicians, computer scientists, statisticians and applied mathematicians. A substantial involvement by all in the details of the data collection and an understanding of the ramifications of the problem is mandatory for the achievement of successful results. The resultant "bootstrapping" method of lifting one's understanding from point to point is not that easily recognized as a virtue by those who are used to thinking in more quantitative veins. If one is attempting to analyze the effects of a drug like penicillin, which revolutionized the treatment of pneumococal pneumonia, then one has single variable effect with a very positive result that is not at all difficult to support statistically. However, in the very difficult area of clinical management of the critically ill patient, one is dealing with the effect of multiple intercurrent diseases and a complex interacting physiologic response pattern. Gains in survival are made by small percentages. One seeks to obtain detailed information concerning the nature and pattern of response that can lead to a more rational and physiologically relevant approach to clinical care.

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