



Noninvasive Autonomic and Hemodynamic Monitoring in Severe Sepsis

ABSTRACT

OBJECTIVES

To evaluate the effects of sympathetic (SNS) and parasympathetic nervous system (PSNS) activity, monitored by heart rate (HR) and respiratory rate (RR) variability, on simultaneously monitored hemodynamic patterns of early severe sepsis and septic shock.

We evaluated the temporal hemodynamic and autonomic nervous system (ANS) activity patterns in:

- a) trauma patients with sepsis,
- b) postoperative patients with sepsis, and
- c) sepsis as the primary etiologic event compared with sepsis as a secondary complication of trauma or surgery.

METHODS

We monitored the spectrum of HR and RR variability simultaneously with noninvasive hemodynamic patterns in 228 septic patients beginning shortly after admission to the emergency department (ED) in a level 1 university-run trauma service. Spectral analysis of HR and RR variability revealed low frequency areas (Lfa), mostly indicating SNS activity, and respiratory (or high) frequency areas (Rfa), indicating PSNS activity. Noninvasive hemodynamic monitoring provided on-line visual displays of developing hemodynamic patterns of cardiac, pulmonary, and tissue perfusion functions.

RESULTS

Spectral analysis of HR and RR variability revealed high Lfa and Rfa values, indicating increased SNS and PSNS activity. The survivors' early autonomic patterns were associated with increased cardiac index (CI), and HR, normal mean arterial pressure (MAP), arterial hemoglobin saturation (SapO₂), and tissue perfusion reflected by PtcO₂/FiO₂ ratios. Nonsurvivors' patterns consisted of normal or slightly elevated CI, hypotension, tachycardia, reduced tissue perfusion, low SapO₂, and reduced oxygen delivery (DO₂). Sudden surges of ANS activity were immediately followed by increased HR, MAP, and CI, and reduced tissue perfusion, especially in nonsurvivors. The opposite hemodynamic changes occurred after abrupt decreases in SNS and PSNS activities.

CONCLUSION

SNS and PSNS activity increased early in sepsis and preceded the pattern of hemodynamic changes. Surges in ANS activity, which were greater in the nonsurvivors, may play a regulatory role in the hemodynamic responses to sepsis.

INTRODUCTION

Spectral analysis of heart rate variability (HRV) is an established method to evaluate the sympathetic nervous system (SNS) activity. Spectral analysis of the respiratory component (RRV) - as a measure of the parasympathetic nervous system (PSNS) - was not initially accepted because of the wide range of respiratory rates (RR). However, Akselrod et al. developed a unique approach to assess both arms (HRV and RRV) of the autonomic nervous system (ANS) activity through spectral analysis. This approach provided objective methods to evaluate both SNS and PSNS activity noninvasively, independently and simultaneously with hemodynamic patterns.

ANS activities may also be affected by associated clinical conditions such as: blood loss, dehydration, sedation, pain, therapy, extent of injury, delay in correcting hypovolemia, and delays in the surgical repair of injuries. A preliminary study of HRV in mild trauma by Fathizadeh et al. demonstrated that ANS activities would function as a precursor to hemodynamic changes. That is, surges of autonomic activity preceded the increases in Heart Rate (HR), Mean Arterial Pressure (MAP), and Cardiac Index (CI), and reductions in tissue perfusion.

Studying the ANS activities may be of extreme significance in acute emergencies where the most urgent problem is to recognize and treat, at the earliest possible time, the circulatory abnormalities leading to shock. Shock after high-risk surgery, trauma, dehydration, sepsis, burns, stroke, acute cardiac conditions, and other acute emergencies are circulatory conditions that can be described by early noninvasive hemodynamic monitoring while they are still readily reversible. Tissue hypoxia, which has been suggested as the basic underlying problem in shock, has been measured by the net cumulative oxygen debt (VO₂). Crowell and Smith continuously monitored VO₂

in controlled experimental studies in anesthetized and bled animals and showed that those who accumulated an oxygen debt of 100 mL/kg all survived, while those that accumulated a debt of 140 mL/kg all died; the 50 percent value was about 120 mL/kg. They concluded that the major outcome determinant was oxygen debt. Subsequently, it was shown that, prevention or early correction of reduced VO₂ rates lead to a significant reduction of organ failures and deaths.

Oxygen debt has been calculated before, during and after high-risk surgery in a large series of high-risk surgical patients. The patients who survived without organ failure had an average of 9 liters of oxygen debt which lasted an average of 12 hours. The survivors with organ failures had an average oxygen debt of 22 liters that lasted about 24 hours. The nonsurvivors all of whom died with organ failures had continuing oxygen debts averaging 33 liters during the 48-hour observation period. It was concluded from these early studies that oxygen debt was the major hemodynamic finding directly related to outcome, and that early goal-directed therapy was an important first step for improved outcome. Recently, Rivers et al. reported improved outcome in septic patients with goal-directed therapy started in the emergency department (ED) based on noninvasive or minimally invasive monitoring.

To elucidate the role of ANS activities in the developing hemodynamic patterns in patients with severe sepsis and septic shock, we applied these methods to septic patients beginning shortly after their ED admission. Although increased autonomic activity is known to occur with trauma and sepsis, the present report suggests that pronounced surges of increased ANS activity may be a circulatory mechanism regulating hemodynamic patterns of sepsis and trauma.

The present study:

- a) describes the patterns of SNS and PSNS activities during the early course of acute sepsis,
- b) relates these ANS patterns to the evolving temporal hemodynamic patterns,
- c) describes these autonomic and hemodynamic interactions of sepsis both as a primary disease and as a complication of trauma and surgery, and
- d) suggests a regulatory role for autonomic surges in the early hemodynamic patterns of acute sepsis.

Simultaneous monitoring of hemodynamic and ANS activity provide a unique opportunity to study the possible regulatory role of surges of ANS activity in hemodynamic responses to clinical sepsis alone and in combination with trauma or surgery. Multiple continuously monitored noninvasive hemodynamic values in the present study also provide an integrated approach to analysis of time-related patterns of cardiac, pulmonary, and tissue perfusion functions.

METHODS

CLINICAL SERIES

Group S1: Sepsis of Unknown Etiology	N =	178
Group S2: Sepsis Acquired Post-Op	N =	35
Group S3: Community Borne Sepsis	N =	15
Age, Years, Mean \pm SD		39.7 \pm 17.3
Gender, M / F		176 (77%) / 52 (23%)
Survivors / Nonsurvivors		176/52
Mortality		23%
ISS Score:	Survivors	25.4 \pm 11.2
	Nonsurvivors	31.5 \pm 12.3

Table 1
Salient Clinical Feature

We studied 228 severe septic patients [Group S1 (N=178: Sepsis of unknown etiology as tested at admission, Group S2 (N=35): Surgical patients who became septic post-operatively, Group S3 (N=15): Acute community borne sepsis (Table 1) with noninvasive hemodynamic and sympathetic SNS and parasympathetic nervous system (PSNS) activity. Measurements were started shortly after admission to the Emergency Department (ED). Selection of septic patients was based on the following criteria: temperature >38 or < 36 , tachycardia (HR >110 beats/min), wbc $>12,000$ or $<3,000$, and evidence of a septic focus or positive blood cultures. These were on occasion accompanied by an episode of hypotensive shock indicated by systolic blood pressure <100 mmHg and mean arterial pressure < 70 mmHg.

There were 176 (77%) males and 52 (23%) females; 176 survived and 52 died during their current hospitalization; the mortality rate was 23%. Table 1 lists the salient clinical features. Children < 17 years of age were excluded. The Institutional Review Board approved the study.

STUDY DESIGN & MANAGEMENT POLICIES

Trauma patients admitted to the LAC+USC Medical Center were managed by a dedicated full-time, 24h/day, 7 days/week, attending faculty and resident staff. Septic

patients were treated in accordance with established protocols. Continuous noninvasive monitoring began shortly after admission to the emergency department (ED) and continued at intervals as the patient went to the radiology department, to the operating room, and to the ICU. In the present study, we evaluated >40,000 values in >6000 data sets in 228 patients with severe sepsis and septic shock. Invasive monitoring with PA catheters was also used when indicated by clinical conditions after ICU admission. Previous studies documented comparable thermodilution and bioimpedance cardiac index values under similar conditions in the ED, OR, and ICU.

AUTONOMIC MONITORING BY HEART RATE & RESPIRATORY RATE VARIABILITY

Sympathetic and parasympathetic activities were noninvasively monitored by the spectrum of HR and RR variability patterns with the Physio PS software in 60 of these patients concurrently with the continuous hemodynamic monitoring beginning in the period shortly after admission to the ED.

Two types of ANS monitoring were used:

- a) conventional HRV without respiratory analysis, that is accepted by the HRV standards conference that calculates Lfa as the area under the heart rate spectral analysis curve within the frequency range of 0.04 to 0.10 Hz, and
- b) HRV with respiratory analysis to identify the dominant respiratory frequency, which is then used to position the averaging window for the calculations of Rfa.

The Lfa, which is the area under the spectral analysis curve in the frequency range of 0.04 to 0.10 Hz, reflects primarily the tone of the sympathetic nervous system as mediated by the cardiac nerve. However, the cardiac nerve travels with the vagus nerve, and also transmits some parasympathetic activity. The respiratory frequency area (Rfa), which reflects parasympathetic nervous system (PSNS) activity, is a 0.12 Hz-wide frequency range of the heart rate spectrum centered on the fundamental respiratory frequency (FRF) defined by the peak mode of the respiratory power spectrum. It indicates vagal outflow and reflects only parasympathetic activity. When HRV with respiratory analysis are taken together, they provide two independent simultaneous measures needed to analyze the two ANS divisions.

The Lfa/Rfa, or "L/R ratio" represents an arithmetic approach to evaluate sympathetic activity by dividing Lfa, which has mostly sympathetic but some parasympathetic activity, by the Rfa, which has only parasympathetic activity. This ratio suggests the proportion of sympathetic to parasympathetic activity. However, very low Rfa values in the denominator may lead to excessively high L/R ratios, which should not be over interpreted.

The temporal patterns of autonomic data were compared with simultaneously monitored hemodynamic data. We separately evaluated the patients who survived their present hospitalization and those who died during their current hospitalization.

INVASIVE HEMODYNAMIC & OXYGEN TRANSPORT MONITORING

A pulmonary artery (PA) thermodilution catheter (SwanGanz®) was placed in high-risk patients when clinically indicated after ICU admission. Cardiac output was measured by the standard thermodilution method. Systemic arterial blood gas samples were taken at the time of thermodilution measurement, immediately analyzed and used to calculate oxygen delivery (DO_2) by standard formulas. Flow-related variables were indexed to body surface area.

NONINVASIVE CARDIAC OUTPUT MONITORING

A thoracic bioelectric impedance device as soon as possible following ED admission. Four pairs of disposable prewired hydrogen electrodes were appropriately positioned on the skin and the EKG leads were placed across the precordium and left shoulder. A 100 kHz, the outer pairs of electrodes passed 4mA alternating current through the patient's thorax and the inner pairs of electrodes measured the voltage difference. Baseline impedance (Z_0) was calculated from the voltage changes sensed by the inner pairs of electrodes. The first derivative of the impedance waveform (dZ/dt) was calculated from the time-impedance curve. The digital signal processing used time-frequency distributions that increased the signal-to-noise ratio. Measurements of cardiac index (CI), mean arterial pressure (MAP), heart rate (HR), pulse oximetry (SapO_2), transcutaneous O_2 (PtcO_2) and CO_2 (PtcCO_2) tensions, and the fractional inspired oxygen concentration (FiO_2) were continuously monitored, recorded by an interfaced personal computer, and directly filed in a database.

BLOOD PRESSURE & HEART RATE

Mean arterial blood pressures (MAP) were measured with a digital cuff sphygmomanometer. MAP was calculated by the device and recorded at intervals simultaneously with the other values. HR was taken from EKG tracings.

PULSE OXIMETRY

A standard pulse oximeter placed on a finger or toe in the routine fashion was used to measure arterial hemoglobin oxygen saturation ($S_{a}O_2$) continuously. Measurements were monitored continuously and recorded at intervals simultaneously with the other values. When there were major changes in pulse oximetry values, they were compared with arterial oxygen saturation obtained by routine blood gas analyses.

TRANSCUTANEOUS O_2 & CO_2 MONITORING

Mean arterial blood pressures (MAP) were measured with a digital cuff sphygmomanometer. MAP was calculated by the device and recorded at intervals simultaneously with the other values. HR was taken from EKG tracings.

STATISTICS

The mean and SEM of each variable at comparable time periods after ED admission were calculated using the GraphPad Prism statistical program. For data of variables collected to compare continuous variables at comparable temporal conditions, we used the two-tailed Student's t-test with the Bonferroni's correction; significant differences were confirmed by the Mann-Whitney U test. Probability values < 0.05 were considered significant.

RESULTS

TEMPORAL AUTONOMIC & HEMODYNAMIC PATTERNS OF SURVIVING AND NONSURVIVING SEPTIC PATIENTS

Table 2 lists the mean \pm SEM of autonomic and hemodynamic values during the first 24 hours after ED admission for 176 surviving and 52 nonsurviving septic patients; the mortality was 23%. Figure 1 illustrates the temporal patterns of these variables during the first 2 - 4 days after ED admission. The early nonsurvivors' Lfa and Rfa values were higher than those of the survivors' values indicating pronounced SNS and PSNS activity at this time. However, in their late or preterminal state, which began about 72 hours after ED admission, the nonsurvivors had near zero values for Lfa and Rfa, indicating that the power or tone of both ANS branches may be exhausted by the late stage. By contrast, the survivors had elevated Lfa and Rfa values in this late period. The L/R ratio was higher in the survivors throughout the period of observation (Table 2).

	Survivors Mean \pm SEM	N	Nonsurvivors Mean \pm SEM	N	P-value
Lfa, (bpm) ²	3.32 \pm 0.62	55	4.78 \pm 1.38	18	0.27*
Rfa, (bpm) ²	4.83 \pm 1.38	55	13.34 \pm 4.64	18	0.012
L/R ratio	8.68 \pm 2.11	55	1.23 \pm 0.22	18	0.048
CI, l/min/m ²	4.03 \pm 0.02	140	3.55 \pm 0.02	38	0.02
HR, bpm	113 \pm 1	140	112 \pm 1	38	0.61*
MAP, mmHg	85 \pm 1	140	83 \pm 1	38	0.29*
SapO ₂ , %	98 \pm 1	140	98 \pm 1	38	0.87*
PtcO ₂ /FiO ₂	175 \pm 2	140	129 \pm 3	38	0.01
DO ₂ , ml/min/m ²	623 \pm 11	52	558 \pm 17	22	0.01

Table 2

Survivors' and Nonsurvivors' Autonomic and Hemodynamic Values during the first 24 hours after onset of Sepsis.

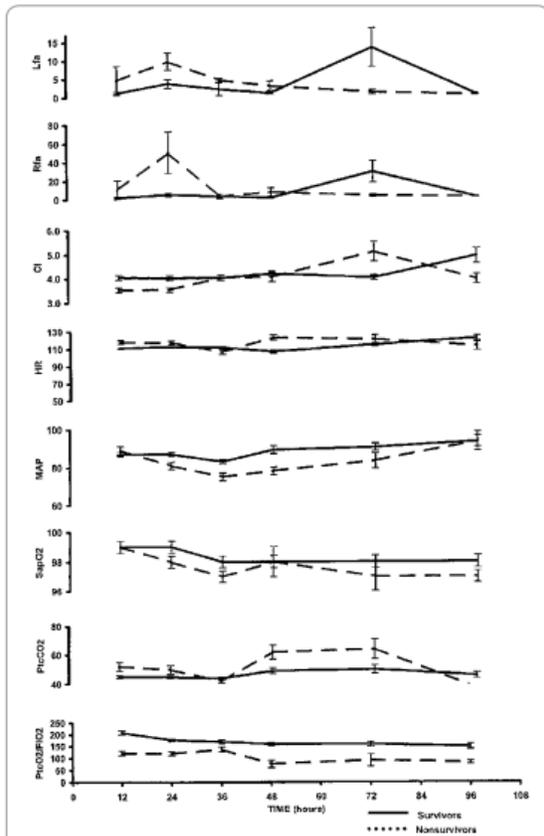


Figure 1: Temporal hemodynamic and autonomic patterns in a series of 178 severely septic patients aligned from the time of ED admission. The patterns of 140 survivors (solid line) and 38 nonsurvivors (dashed line) are shown. Note: in the early period, the Lfa and Rfa were higher in the nonsurvivors; the CI, MAP, SapO₂, and PtcO₂/FiO₂ ratio were usually higher in the survivors throughout the period of observation.

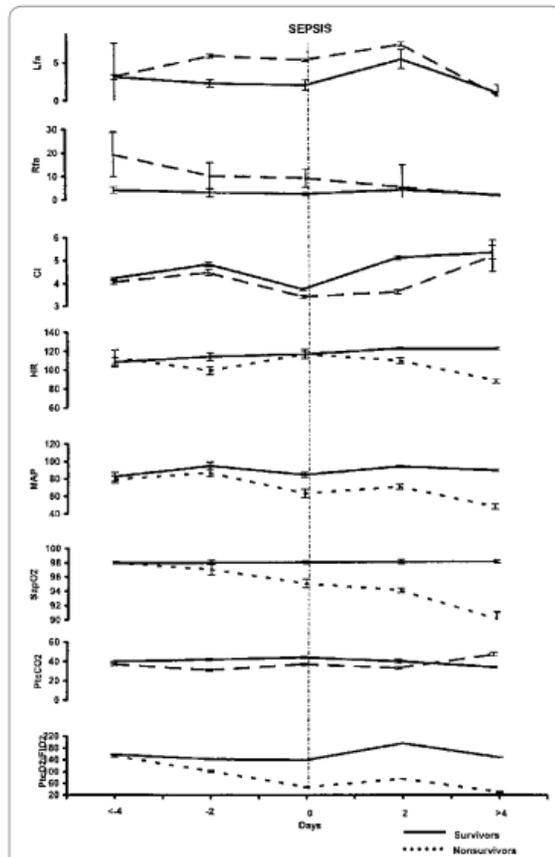


Figure 2: Temporal autonomic and hemodynamic patterns of survivors (solid line) and nonsurvivors (dashed line) before and after the clinical onset of severe sepsis indicated by the vertical dashed line. Note: the Lfa and Rfa values were higher in nonsurvivors, while the CI, MAP, SapO₂, and PtcO₂/FiO₂ ratio were higher in the survivors before and after onset of sepsis.

The survivors had mean CI values of 4 liters/min/m² for the first 24 hours after admission. This was significantly higher than the nonsurvivors' relatively normal cardiac index values of 3.75 liters/min/m² in the initial period, but after 72 hours, the CI rose to a mean of about 5 liters/min/m² in both groups (Figure 2). The HR was elevated in both groups. The blood pressure, PtcO₂, and PtcO₂/FiO₂ ratio were normal for the survivors but lower in the nonsurvivors during the early period. The SapO₂ values were lower in nonsurvivors in the initial period. The DO₂ values were higher in the survivors (Table 2).

AUTONOMIC PATTERNS AT VARIOUS STAGES OF SEPSIS & RECOVERY

The Lfa and Rfa values were higher in the nonsurvivors in the early (first 24-h) and middle (2 to 4 days after ED admission) periods (Table 2). The nonsurvivors' Lfa and Rfa values dropped to very low levels in their late or terminal period.

	Mean ± SEM	AT MAXIMUM	CHANGE	P-VALUE
		Mean ± SEM	Mean ± SEM	
Lfa, (bpm) ²	2.67 ± 4.18	35.9 ± 9.96	33.2 ± 5.6	0.002
Rfa, (bpm) ²	3.01 ± 3.8	70.6 ± 37.5	67.6 ± 33.9	0.05
L/R ratio	2.1 ± 0.5	1.5 ± 0.4	-0.66 ± 0.6	NS*
CI, L/min/m ²	3.77 ± 0.95	4.87 ± 1.51	1.10 ± 0.13	0.05
HR, bpm	110 ± 18	119 ± 17	9±3.2	0.05
MAP, mmHg	74 ± 21	88 ± 25	14 ± 6	0.06
PtcO ₂ /FiO ₂	168 ± 57	133 ± 49	-35 ± 18	0.05

* Not Significant; Lfa low frequency area, Rfa respiratory frequency area, L/R ratio Lfa/Rfa, CI cardiac index, HR heart rate, MAP mean arterial pressure, PtcO₂ / FiO₂ transcutaneous O₂ tension indexed to the fractional inspired oxygen concentration (FiO₂).

Table 3
Values of Sudden Surges of Increased Autonomic Function (N=228)

	At Maximum (N=228)	Post-maximum baseline (228)	CHANGE	P-VALUE
	Mean ± SEM	Mean ± SEM	Mean ± SEM	
Lfa, (bpm) ²	22.3 ± 8	1.8 ± 0.6	-20.5 ± 7.6	0.01
Rfa, (bpm) ²	36.7 ± 16	3.8 ± 1.7	-32.9 ± 15.4	0.04
L/R ratio	7.5 ± 5.4	6.7 ± 5.0	-0.7±0.9	NS*
CI, L/min/m ²	4.36 ± 0.27	3.52 ± 0.26	-0.83 ± 0.16	0.03
HR, bpm	114 ± 4.8	105 ± 5	-9.0 ± 3	0.05
MAP, mmHg	92 ± 4	92 ± 4	-12 ± 3	0.03
PtcO ₂ /FiO ₂	163 ± 23	202 ± 21	39 ±12	0.05

* Not significant; Lfa low frequency area, Rfa respiratory frequency area, L/R, Lfa/Rfa ratio, CI cardiac index, HR heart rate, MAP mean arterial pressure, PtcO₂ /FiO₂, transcutaneous O₂ tension indexed to the fractional inspired oxygen concentration (FiO₂).

Table 4
Autonomic and Hemodynamic Values at Periods of Reduced Autonomic Function

HEMODYNAMIC CHANGES AFTER SUDDEN INCREASED OR DECREASED AUTONOMIC FUNCTION

We observed most changes in hemodynamic patterns in the first 48 hours after ED admission occurred after sudden major increases or surges in autonomic functions, indicated by abrupt increases in Lfa and Rfa values (Table 3). Marked increases in autonomic activity preceded by 20 to 40 seconds significant increases in CI, HR, and MAP, and reduced tissue perfusion, indicated by reduced PtcO₂ /FiO₂ ratios. Changes in opposite directions were noted after sudden reductions in autonomic function (Table 4). Abruptly reduced Lfa and Rfa values were associated with decreased CI, HR, and MAP, and higher PtcO₂ /FiO₂ values.

AUTONOMIC & HEMODYNAMIC PATTERNS OF POSTOPERATIVE PATIENTS WITH SEPSIS

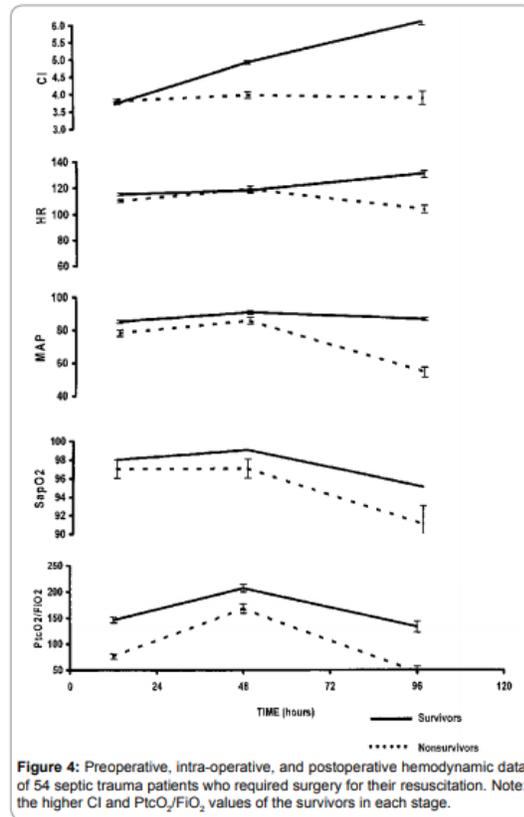
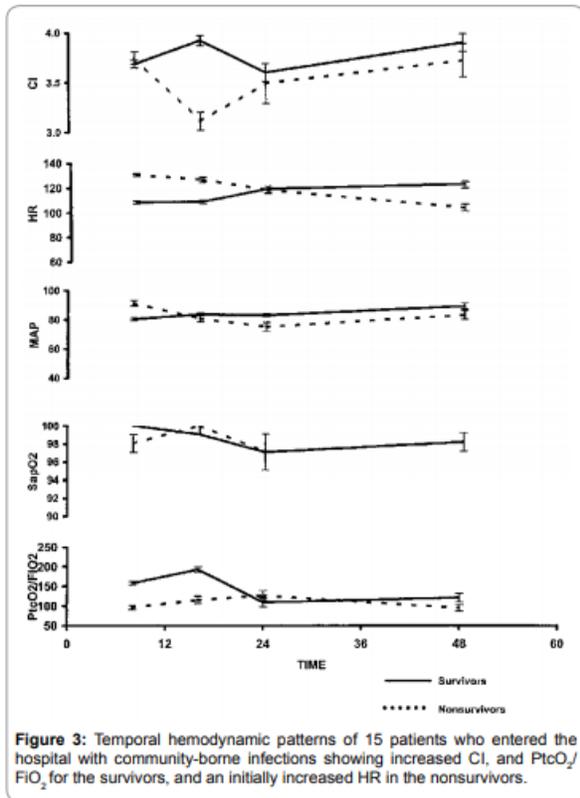
Table 5 lists the values of 35 patients with onset of sepsis as a postoperative complication (Figure 3); illustrates their temporal relationships. The survivors had higher CI, MAP, and PtcO₂ /FiO₂ values than did the nonsurvivors, and the nonsurvivors had higher Lfa and Rfa values.

	Survivors (N=24) Mean ± SEM	Nonsurvivors (N=11) Mean ±SEM	P-value
Lfa, (bpm) ²	1.08 ± 0.12	3.42 ± 0.88	0.001
Rfa, (bpm) ²	1.33 ± 0.22	4.79 ± 0.98	0.001
L/R ratio	10.4 ± 2.52	1.2 ± 0.20	0.02
CI, L/min/m ²	3.9 ± 0.03	3.5 ± 0.06	0.05
HR, bpm	106 ± 1	104 ± 1	NS*
MAP, mmHg	87 ± 1	73 ± 1	0.001
SapO ₂ , %	98 ± 1	96 ± 1	NS*
PtcO ₂ /FiO ₂	179 ± 3	112 ± 5	0.001

* Not significant; Lfa low frequency area, Rfa respiratory frequency area, L/R, Lfa/Rfa ratio, CI cardiac index, HR heart rate, MAP mean arterial pressure, SapO₂ arterial hemoglobin saturation, PtcO₂ /FiO₂ transcutaneous O₂ tension indexed to fractional inspired oxygen concentration (FiO₂).

Table 5

Autonomic and Hemodynamic Values in Survivors and Nonsurvivors with Sepsis as a Complication of Trauma during the first 48-hours after ED admission



PERI-OPERATIVE PATTERNS OF SEPTIC PATIENTS WHO UNDERWENT SURGERY

Figure 4 illustrates the hemodynamic data of 54 septic trauma patients who required surgery as part of their resuscitation. Note: the higher CI and $PtcO_2/FiO_2$ values of the survivors in the preoperative, intra-operative, and postoperative stages.

PATTERN OF SEPSIS AS THE PRIMARY ETHIOLOGIC EVENT VERSUS SEPSIS AS A SECONDARY COMPLICATION

Figure 4 describes the temporal patterns of 15 patients who on ED admission had sepsis from community-borne infections without evidence of significant trauma. The survivors had higher CI, MAP, and $PtcO_2/FiO_2$. Table 5 summarizes the data of 35 patients who had developed sepsis as a postoperative complication. The nonsurvivors had higher Lfa, Rfa, and L/R ratios, while the survivors had higher CI, MAP, SpO_2 , and $PtcO_2/FiO_2$ values than did the nonsurvivors. Table 6 shows the CI, MAP, and HR values in 4 nonsurviving and 5 surviving trauma patients who were observed before and immediately after onset of an acute septic complication.

	Survivors (N=5) Mean ± SEM		P-VALUE	Nonsurvivors (N=4) Mean ± SEM		P-VALUE
	BEFORE	AFTER		BEFORE	AFTER	
CI, L/min/m ²	4.24 ± 0.15	4.43±0.13	NS	3.54 ± 0.04	4.42±0.13	0.001
HR, bpm	104 ± 3	101±2	NS	92 ± 1	106±3	0.004
MAP, mmHg	103 ± 2	87±2	0.001	82 ± 2	68±2	0.003
SapO ₂ , %	98 ± 1	98±0	NS	97 ± 1	94±1	NS*
PtcCO ₂ , torr	38 ± 1	43±2	NS	60 ± 2	63±2	NS*
PtcO ₂ /FiO ₂	163 ± 14	144±5	NS	82 ± 8	60±6	NS*

Table 6

Data of patients immediately before and after a Septic Complication of Trauma

DISCUSSIONS

This study focuses on the early temporal patterns from the time of ED admission of HR and RR variability as measures of ANS activity and their relationship to hemodynamic patterns in surviving and nonsurviving septic patients. We evaluated the early patterns of ANS and hemodynamics in sepsis separately from the effects of trauma and surgery.

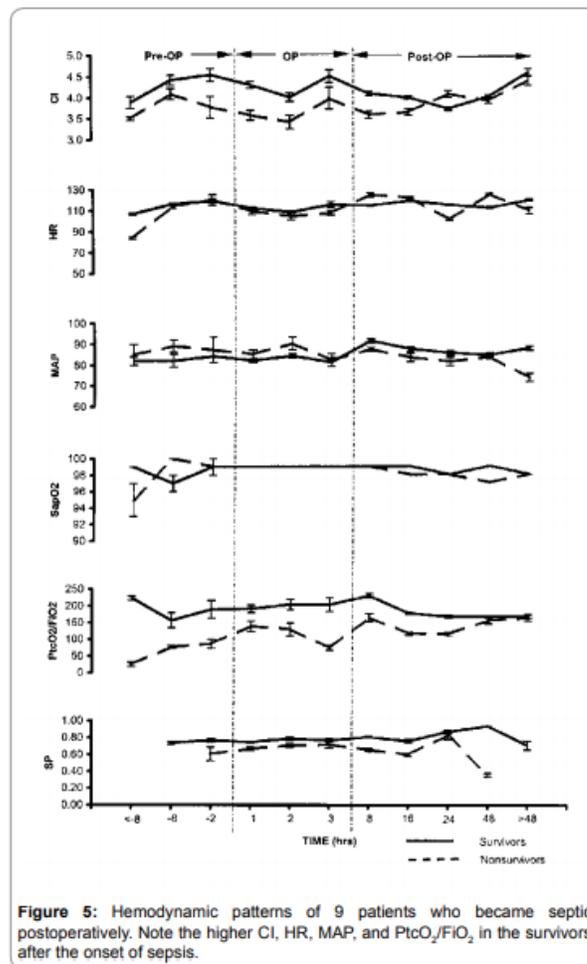
The results of the present study indicate that:

- a) the survivors of sepsis had greater CI, MAP, SaO₂, PtcO₂ /FiO₂, and DO₂ than did the nonsurvivors;
- b) in the early period of nonsurviving septic patients, the Lfa and Rfa values were significantly elevated compared with those of the survivors, possibly because the nonsurvivors needed more ANS activity to maintain or compensate for their impaired hemodynamic status;
- c) hemodynamic patterns appear to be regulated by sudden abrupt surges of both SNS and PSNS activities, which were immediately associated with higher CI, MAP, and HR and decreased PtcO₂ /FiO₂;
- d) the opposite hemodynamic effects occurred at the cessation of the ANS surges; and
- e) the Rfa values were more elevated than the Lfa values in sepsis, suggesting that increased parasympathetic activity in septic nonsurvivors was at least as active, and probably more active, than the sympathetic activity.

The Lfa and Rfa patterns of ANS activities in surviving and non surviving septic patients were similar to those of trauma patients. Increased parasympathetic tone was not unexpected in septic patients, since increased PSNS activity is known to be involved in the recovery process of cardiac patients. The elevated Lfa and L/R ratio resulting from increased sympathetic activity is similar to the stress response to trauma due to uneven metarteriolar vasoconstriction and appears to follow surges of sympathetic and parasympathetic activity. Elevation of both Lfa and Rfa after sepsis as well as trauma indicates increased SNS and PSNS activity that leads to localized redistribution of flow from metarteriolar vasoconstriction. The uneven metarteriolar vasoconstriction results in uneven tissue perfusion with local areas of reduced tissue perfusion and oxygenation. In shock, progressively increasing areas of flow maldistribution contribute to increasing tissue hypoxia that leads to global tissue hypoxia, a physiologic hallmark of shock. There also were differences in the patterns of flow (CI) and tissue perfusion ($PtcO_2 / FiO_2$) between septic survivors and nonsurvivors after high-risk surgical operations (Figure 4).

The terminal state in septic patients was marked by progressive fall in CI, MAP, DO_2 , and $PtcO_2 / FiO_2$ values with increased HR, followed by bradycardia, and increased $PtcCO_2$ values. The $PtcO_2 / FiO_2$ values of zero or near zero with high $PtcCO_2$ values in extremely ill and dying patients are indicative of the global tissue hypoxia of shock.

High-risk surgery, trauma, and sepsis have been shown to stimulate hemodynamic function as indicated by increased CI, MAP, HR, and DO_2 . When trauma was complicated by sepsis, body metabolism increased possibly by the increased ANS activity as well as by various immunochemical mechanisms. The increased CI, MAP, $PtcO_2 / FiO_2$, and DO_2 of the survivors is consistent with the concept that they are compensatory hemodynamic responses that have survival value (Figure 5).



The ANS data are consistent with the concept that increased values of both Lfa reflecting mostly sympathetic activity and Rfa representing parasympathetic activity occur with sepsis as well as trauma, and surgery. The data also suggest that increased autonomic activity is an important regulatory mechanism for the developing hemodynamic patterns. However, intense SNS activity may also lead to uneven met arteriolar vasoconstriction that alters the distribution of microcirculatory flow and may limit local tissue oxygenation. Tissue perfusion/oxygenation depends on both the overall blood flow (CI), as well as the even distribution of microcirculatory blood flow needed to oxygenate local tissues. PtcO₂ /FiO₂, which is a direct measure of local tissue oxygenation, may be a useful marker of the adequacy of tissue perfusion/oxygenation in posttraumatic states.

The major limitations of this study, like most initial inquiries into previously unexplored fields, are that it is largely a descriptive study in a relatively small group of septic patients with suggestive evidence of underlying circulatory mechanisms. It is underlined that this by no means is some form of a randomized clinical trial designed as such from its initial steps so that we could enroll patients in a 1:1:1 allocation ratio for the arms studied. We also fully comprehend that as per ISS scores, the 3 arms may have been

incomparable at admission, in terms of trauma severity, indeed, this was also indicated by our basic statistics comparisons, yet, ANS patterns/responses (in terms of signal analyses) did not suggest significant differences. We cannot exclude the aberration from the 1:1:1 allocation ratio as possibly responsible for this effect. Hence, we do not report pertinent analyses and outcomes.

The ANS patterns we studied were associated with simultaneously monitored hemodynamic patterns in a variety of clinical septic conditions, but not causally related to them. However, the temporal ANS and hemodynamic patterns, if confirmed, may lead to future therapeutic questions that are testable in controlled clinical trials. Notably, significant work has been generated lately investigating HRV in acute conditions. Yet, more data are needed on the ANS role in regulating hemodynamic patterns of various septic, traumatic, surgical, and hemorrhagic states.

The present study suggests possible therapeutic approaches to ANS support for optimal hemodynamic patterns in septic and traumatic states. As has been shown in high-risk elective surgery, the hemodynamic patterns of the surviving patients may be a reasonable first approximation to the definition of optimal goal-directed therapy. The components of goal-directed therapy may be evaluated by their capacity to achieve optimal goals and to improve outcome. In the process of evaluation of therapy, the efficacy of various administered agents also may suggest underlying physiologic mechanisms.

ABBREVIATIONS USED

ABBREVIATION	TERM
ANS:	Autonomic Nervous System
DO2 :	Oxygen Delivery
CI:	Cardiac Index
ED:	Emergency Department
FiO2 :	Fractional Inspired Oxygen Concentration
HRV:	Heart Rate Variability
Lfa:	Low Frequency Area
L/R (or Lfa/ LRfa) ratio:	Low Frequency Area / Respiratory Frequency Area Ratio
PAOP:	Pulmonary Artery Occlusion Pressure
PSNS:	Parasympathetic Nervous System
SNS:	Sympathetic Nervous System
PtcCO2 :	Transcutaneous Carbon dioxide Tension
PtcO2 /FiO2 :	Transcutaneous Oxygen Tension indexed to FiO2
Rfa:	Respiratory Frequency Areas
RR:	Respiratory Rate
RRV:	Respiratory Rate Variability
SapO2 :	Arterial Hemoglobin Oxygen Saturation by Pulse Oximetry
VO2 :	Oxygen Consumption