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Autonomic and Hemodynamic Activity in Sepsis

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ABSTRACT

Objectives: The aim is to evaluate early hemodynamic patterns of patients with severe sepsis and septic shock and compare/contrast the effects of sepsis as a primary etiologic event versus sepsis as a secondary complication after trauma, surgery etc. with simultaneously monitored sympathetic (SNS) and parasympathetic nervous system (PSNS) activities measured by the variability of the heart rate (HR) and respiratory rate (RR).

Setting: Level 1 university-run trauma service in a public hospital.

Methods: Non-invasively monitored the early hemodynamic patterns in 208 severely septic patients beginning shortly after admission to the emergency department (ED). Simultaneously, monitored and compared the spectrum of HR and RR variability patterns, as markers of autonomic activity, with temporal hemodynamic patterns in 73 of these septic patients. The HR variability was measured to evaluate the low frequency area (LFa), which reflects SNS. The high frequency area (RFa) is indicative of PSNS activity. The LFa/RFa, reflects the relationship of SNS to PSNS. Concurrent noninvasive hemodynamic monitoring consisting of: a) cardiac output by bioimpedance, HR, and mean arterial pressure (MAP) to reflect cardiac function, b) pulse oximetry ($SapO_2$) to reflect changes in pulmonary function, and c) transcutaneous oxygen ($PtcO_2$) indexed to the FiO_2 as a marker of tissue perfusion/oxygenation.

Results: Non-survivors had higher LFa and RFa values than the survivors did. The increased RFa preceded the increases in LFa in non-survivors and a higher percentage of sympathetic activity. These changes were more marked when measured before sedation and pain medication. In survivors, these patterns were associated with increased cardiac index (CI), and HR, normal MAP, $SapO_2$, and normal tissue perfusion indicated by $PtcO_2/FiO_2$ ratios. Nonsurvivors had relatively normal CI, hypotension, tachycardia, poor tissue perfusion, borderline $SapO_2$, and reduced oxygen delivery.

Conclusions: In the period immediately after ED admission of patients with sepsis increased ANS activity was observed more pronounced in non-survivors. This ANS activity was associated with increased HR, MAP, and CI, and a tendency toward reduced tissue perfusion/oxygenation.

INTRODUCTION

The aims were to evaluate early hemodynamic patterns of surviving and nonsurviving patients with severe sepsis and septic shock. Second, to compare these hemodynamic patterns with simultaneously monitored sympathetic (SNS) and parasympathetic nervous system (PSNS) activities measured by the variability of the heart rate (HR) and respiratory rate (RR); collectively known as autonomic nervous system (ANS) monitoring. Third, to compare and contrast the effects of sepsis as a primary etiologic event versus sepsis as a secondary complication after trauma, surgery, and other acute illnesses with simultaneously monitored SNS and PSNS activities measured by ANS monitoring.

The present study: a) describes the patterns of sympathetic and parasympathetic activities in acute sepsis, b) relates these to the evolving temporal hemodynamic patterns, and c) describes these autonomic and hemodynamic interactions in sepsis as a primary disease, and as a complication of trauma and surgery. Rivers et al (11) showed improved outcome in septic patients with goal-directed therapy started in the emergency department (ED) based on minimally invasive monitoring. Multiple continuously monitored noninvasive hemodynamic values used in the present study provided an integrated approach to major circulatory components: cardiac, pulmonary, and tissue perfusion functions (6,8,12-21). Simultaneous measurements of hemodynamics with ANS activity provide a unique opportunity to study the role of ANS activity in the hemodynamic responses to various clinical septic conditions alone and in combination with surgery, trauma, or other acute emergencies.

METHODS

Clinical Series

We studied 208 consecutively monitored severe septic patients with noninvasive hemodynamic and autonomic (sympathetic and parasympathetic) nervous system activity. Measurements were started shortly after admission to the Emergency Department (ED) of a level 1 university-run trauma service in a large inner city public hospital. Patient selection 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 usually accompanied by an episode of hypotension (systolic blood pressure <100 mmHg or mean arterial pressure < 70 mmHg).

There were 160 (77%) males and 48 (23%) females; 160 survived and 48 died during their current hospitalization; the mortality was 23%. Table 1 lists demographic and salient clinical features. Children < 17 years of age were excluded. The Institutional Review Board approved the study.

TABLE 1: Salient clinical features.

Age, Years, Mean ± SD	39.7 ± 17.3
Sex, M/F, (%)	160(77%)/48 (23%)
Survivors/Nonsurvivors (% mortality)	160 /48 (23%)
Survivors ISS score	25.4 ± 11.2
Nonsurvivors ISS score	31.5 ± 12.3

Study Design and 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 in the emergency department (ED) and continued as the patient went to the radiology department, to the operating room, and then into the ICU. Invasive monitoring with PA catheters was also used for hemodynamic measurements after ICU admission when indicated by clinical conditions. Serial thermodilution cardiac output values were measured at frequent intervals according to clinical need. In the present study, we evaluated a total of >40,000 values in >6000 data sets in 208 patients with severe sepsis and septic shock. Previous studies documented comparable thermodilution and bioimpedance cardiac index values under similar conditions (6,14).

Autonomic Monitoring by Heart Rate Variability

Sympathetic and parasympathetic activities were measured by the Ansar ANX-3.0 autonomic nervous system monitor (Philadelphia, PA) beginning in the period immediately after admission to the ED (1-5,9,10). The HR and RR variability were analyzed by spectral analysis in the frequency domain to evaluate the low frequency (Lfa), and the higher (on the frequency axis) respiratory frequency (Rfa) areas of variability. The Lfa is the area under the spectral analysis curve within the frequency range of 0.04 to 0.10 Hz. This area reflects primarily the tone of the sympathetic nervous system. The respiratory frequency area (Rfa) is a 0.12 Hz-wide frequency range centered on the fundamental respiratory frequency (FRF). The latter was defined by the peak mode of the respiratory power spectrum. It is indicative of vagal outflow. The Rfa reflects only parasympathetic nervous system activity. The Lfa/Rfa, or "L/R ratio, represents sympathovagal balance, the relative measure of both sympathetic and parasympathetic activities (2-5). Normal (stable) data are presented in Table 2.

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

TABLE 2: Sample ranges of normal (stable) and abnormal for the three parameters subserving ANS monitoring. Data from Estefanos *et al.* (32) 1991 Cleveland Clinic Study of 27 normal healthy adult volunteers (age = 30 ± 2.0 yrs) followed for 4 months. Subjects with abnormal responses were rejected. The 27 are those that were not rejected. Subjects' results at 30° tilt were statistically the same as supine ($p<0.01$). LFa and RFa values carry units of power (bpm^2), the ratio is dimension-less. (From Estaferan, Personal communication).

	Lfa	**Rfa**	**Ratio**
Stable (supine)	5.20 ± 1.0	2.17 ± 0.5	2.40 ± 0.5
Stable (60° Tilt)	15.7 ± 2.5	1.33 ± 0.92	11.8 ± 2.3
Post-injury recovery	2.19 ± 0.43	2.23 ± 0.60	4.38 ± 1.02

Invasive Hemodynamic and Oxygen Transport Monitoring

A pulmonary artery (PA) thermodilution catheter (Swan-Ganz ^{R}) was placed in high-risk patients on admission to the ICU. Cardiac output was measured by the standard thermodilution method. Arterial and mixed venous blood gas samples were sampled at the time of thermodilution measurement, immediately analyzed and used to calculate oxygen delivery (DO_2) and oxygen consumption (VO_2) by standard formulas (6,14). Flow-related variables were indexed to body surface area.

Noninvasive Cardiac Output Monitoring

A thoracic bioelectric impedance device (IQ System, Noninvasive Medical Technologies, LLC, Henderson, NV) was applied as soon as possible following ED admission. Four pairs of disposable prewired, hydrogel electrodes were appropriately positioned on the skin and three EKG leads were placed across the precardium and left shoulder (12-14). 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 (Zo) 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 EKG and bioimpedance signals were filtered with an all-integer-coefficient technology to decrease computations and signal processing time. The digital signal processing used time-frequency distributions that increased the signal-to-noise ratio (12-14). Measurements of cardiac index (CI), heart rate, pulse oximetry, transcutaneous O_2 and CO_2 tensions, and the fractional inspired oxygen concentration (FiO_2) were continuously monitored, recorded by an interfaced personal computer, and filed directly into a database.

Blood Pressure and Heart Rate

Mean arterial blood pressures (MAP) were measured with a digital cuff sphygmomanometer (Dinamap, Critikon, Tampa, FL). MAP was calculated by the device and recorded at intervals simultaneously with the other values. Heart rates were taken from EKG tracings (6).

Pulse Oximetry

A standard pulse oximeter (Nellcor, Pleasanton, CA) placed on a finger or toe in the routine fashion was used to measure arterial hemoglobin oxygen saturation ($SapO_2$) 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 (6).

Transcutaneous O_2 and CO_2 Monitoring

The patients were continuously monitored with transcutaneous $PtcO_2$ and $PtcCO_2$ sensors (Respironics, Inc., Youngwood, PA) in a standardized fashion. After cleaning the skin with alcohol, a gel electrolyte was applied to the sensor and the sensor was fixed by an adhesive ring the skin on the anterior chest wall or shoulder depending on area of injury and surgical procedure. A two-point gas calibration was done and 20 minutes was allowed for the sensors to equilibrate. Every 4 hours, the $PtcO_2$ and $PtcCO_2$ sensors were placed on a nearby skin location to avoid electrode induced first degree skin burns, re-calibrated, and allowed to equilibrate (15-21). $PtcO_2$ was measured continuously, recorded at standard intervals by an interfaced personal computer, and filed directly into a database. $PtcO_2$ values measured in torr, indexed to FIO_2 and expressed as the ratio, $PtcO_2/FiO_2$. Transcutaneous carbon dioxide ($PtcCO_2$) tension of the skin surface was monitored with the standard Stowe-Severinghaus electrode (17,18).

Statistics

The mean and standard deviations of each variable at comparable time periods after ED admission were calculated using the GraphPad Prism statistical program. Data sets were evaluated using the two-tailed Student's t-test. Differences were considered significant at probability values <0.05.

RESULTS

The mean $\pm$ SEM autonomic and hemodynamic values for survivors and nonsurvivors of sepsis are listed in Table 3. The nonsurvivors' Lfa and Rfa values were higher than those of the survivors values indicating pronounced SNS and PSNS activity (Fig. 1 and Table 3). The L/R ratio, which indicates the proportion of sympathetic to parasympathetic activity, was higher in survivors (Fig. 1 and Table 3).

The survivors had mean cardiac index values of 4 liters/min/m^2 for the first four days after admission. This was higher than the relatively normal cardiac index values of the nonsurvivors. Heart rate was elevated in both groups but greater in the nonsurvivors. The blood pressure, $PtcO_2$, and $PtcO_2/FiO_2$ ratio were normal for the survivors but low in nonsurvivors during the period of observation. The arterial hemoglobin saturation ($SapO_2$) values were essentially normal in both groups throughout. The DO_2 and VO_2 were higher in survivors than in the nonsurvivors (Fig. 2 and Table 3).

TABLE 3. Autonomic and Hemodynamic Values in Survivors and Nonsurvivors of Sepsis

	Survivors	**N**	**Nonsurvivors**	**N**	**P-value**
	Mean ± SEM		Mean ± SEM		
Lfa	3.32 ± 0.62	55	4.78 ± 1.38	18	0.27*
Rfa	4.83 ± 1.38	55	13.34 ± 4.64	18	0.012
L/R	8.68 ± 2.11	55	1.23 ± 0.22	18	0.048
CI	4.03 ± 0.02	160	3.75 ± 0.02	48	0.001
HR	113 ± 1	160	112 ± 1	48	0.608*
MAP	85 ± 1	160	83 ± 1	48	0.29*
$SapO_2$	98 ± 1	160	98 ± 1	48	0.001
$PtcO_2/FiO_2$	175 ± 2	160	129 ± 3	48	0.001
DO_2	623 ± 11	52	558 ± 17	22	0.006

* 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, $SapO_2$ arterial hemoglobin saturation, $PtcO_2/FiO_2$ transcutaneous O_2 tension indexed to the fractional inspired oxygen concentration (FiO_2), DO_2 Oxygen delivery, VO_2 Oxygen consumption.

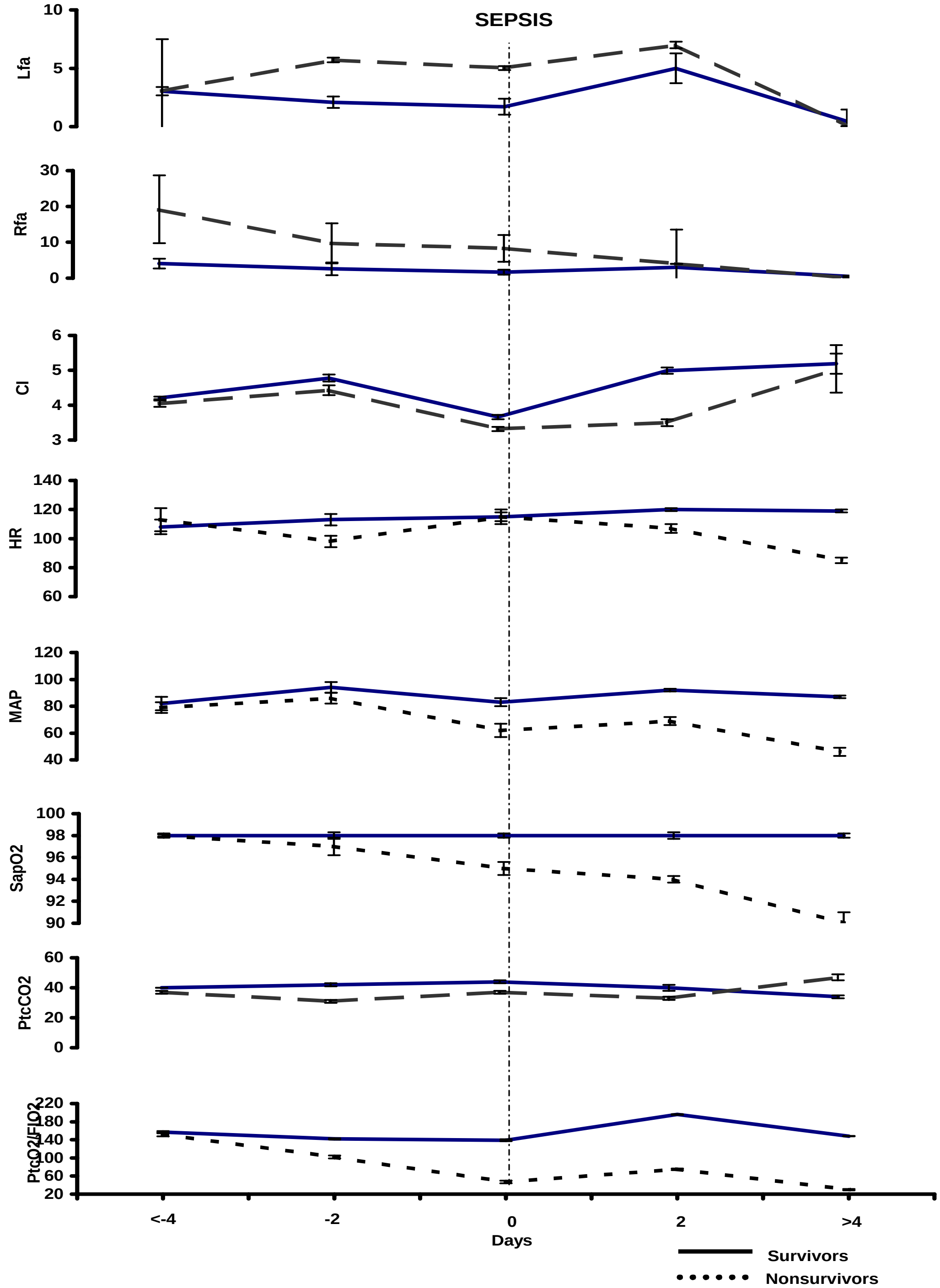

FIGURE 1. Temporal hemodynamic and autonomic patterns before and after the onset of sepsis, indicated by the vertical dashed line. The patterns of survivors (solid line) and nonsuvivors (dashed line) are shown before and after the onset of sepsis. Note the Lfa and Rfa are higher in the nonsurvivors before and after the clinical onset of sepsis, and there are higher CI, MAP, $SapO_2$, and $PtcO_2/FiO_2$ ratio for the survivors during the period of observation.

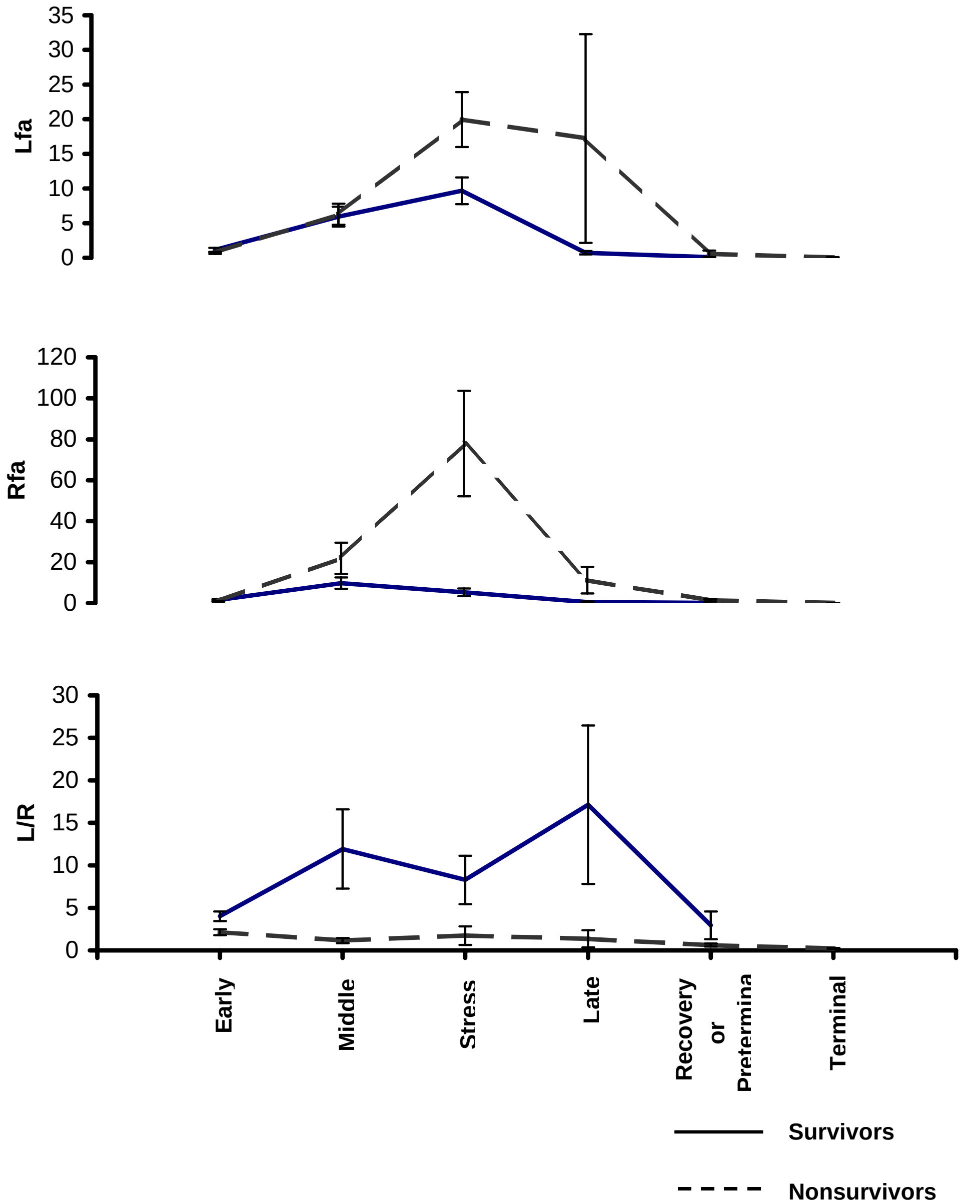

FIGURE 2. Lfa, Rfa, and L/R ratio patterns at various stages of severe sepsis for survivors and nonsurvivors.

DISCUSSION

Non-survivors had higher LFa and RFa values than the survivors suggesting greater autonomic nervous system (ANS) activity. The increased RFa preceded the increases in LFa in non-survivors and was greater in absolute terms than the sympathetic activity. The non-survivors also had a higher percentage of sympathetic activity throughout the period of observation. These changes were more marked when measured before sedation and pain medication. In survivors, these patterns were associated with increased cardiac index (CI), and HR, normal MAP, $SapO_2$, and normal tissue perfusion indicated by $PtcO_2/FiO_2$ ratios. Nonsurvivors had relatively normal CI, hypotension, tachycardia, poor tissue perfusion, borderline $SapO_2$, and reduced oxygen delivery.

CONCLUSION

In the period immediately after ED admission of patients with sepsis increased ANS activity was observed more pronounced in non-survivors. This ANS activity was associated with increased HR, MAP, and CI, and a tendency toward reduced tissue perfusion/oxygenation. The opposite changes in hemodynamic functions occurred during periods of decreasing autonomic activity.