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ANS-BASED EARLY GOAL-DIRECTED THERAPY IN THE TREATMENT OF SEVERE SEPSIS AND SEPTIC SHOCK: PRELIMINARY EVIDENCE

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ABSTRACT

Objective: To investigate the clinical efficacy of early goal-directed therapy based on autonomic nervous system (ANS) monitoring (non-invasive, simultaneous, independent measures of sympathetic (SNS) and parasympathetic nervous system (PSNS) activity) in patients with severe sepsis and septic shock.

Setting: An urban, level 1 university-run trauma service.

Methods: 208 severe sepsis and septic shock patients were studied. ANS monitoring measured the sequential patterns of SNS and PSNS activity immediately after admission to the emergency department (ED). Also measured noninvasive hemodynamic patterns, including: cardiac index (CI) by bioimpedance, as well as HR, and mean arterial pressure (MAP) to evaluate cardiac function, pulse oximetry to reflect changes in respiratory function, and transcutaneous oxygen ($PtcO_2$) to reflect tissue perfusion/oxygenation.

Results: In all patients autonomic balance (the ratio of SNS to PSNS activity) was markedly abnormal. These patients also had low MAP, CI, and $PtcO_2/FiO_2$ values associated with increased HRV that reflect increased autonomic activity. Patients with improved or restored ANS early in their ED stay, all survived; while the latter admission to ED had mixed results. ANS balance was not well-correlated with HR, BP, and CI.

Conclusions: In nonsurvivors, severe sepsis and septic shock were associated with pronounced ANS imbalance. Survivors had relatively normal ANS balance. Patients that first presented poor ANS balance had balance improved due to therapy, also survived.

INTRODUCTION

The aim is to retrospectively investigate the clinical efficacy of early goal-directed therapy based on autonomic nervous system (ANS) monitoring (non-invasive, simultaneous, independent measures of sympathetic (SNS) and parasympathetic nervous system (PSNS) activity) in patients with severe sepsis and septic shock. Our lab has shown evidence of autonomic instability precedes pathology [Fathizadeh, *et al.*, 2004]. Specifically, we have observed autonomic instability preceding and occurring concurrently with Hypovolemia in emergency surgery cases [Dutton, *et al.*, 2001; Zaglaniczny *et al.*, 2000]. Further evidence suggests that resolving the Hypovolemia returns stability to the patient's ANS. It also seems likely that autonomic instability precedes and occurs concurrently with uneven tissue perfusion that can result from sepsis. Lastly, it is known that poor autonomic measures indicate poor outcomes, favorable autonomic measures indicate favorable outcomes, and improved (over time) autonomic measures lead to improved outcomes. Therefore, it is our hypothesis that goal-directed therapy that normalizes tissue perfusion can help to normalize measured autonomic indices and can promote survival.

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). 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 $\pm$ SD	39.7 $\pm$ 17.3
Sex, M/F, (%)	160(77%)/48 (23%)
Survivors/Nonsurvivors (% mortality)	160 /48 (23%)
Survivors ISS score	25.4 $\pm$ 11.2
Nonsurvivors ISS score	31.5 $\pm$ 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 Estefanos, 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

In all cohort patients autonomic balance (the ratio of SNS to PSNS activity) was markedly abnormal (Fig. 1 and Table 3 of CHEST 2005 Poster #601 entitled “Autonomic and Hemodynamic Activity in Sepsis”). These patients also had low MAP, CI, and $PtcO_2/FiO_2$ values associated with increased HRV that reflect increased autonomic activity (Fig. 2 and Table 3 of CHEST 2005 Poster #601 entitled “Autonomic and Hemodynamic Activity in Sepsis”). Average data from all 208 patients are presented here in Fig. 1. Non-survivor’s sympathetic (Lfa) and parasympathetic (Rfa) measures fluctuated through out the first days post-admission. The survivor’s measures peaked once, early, and then normalized. From the standard error bars, it seems as if the parasympathetic data are more definitive, the standard error ranges do not overlap as they do for the sympathetic data. Overall, the survivors’ autonomic measures were more in the normal (stable) range (compare ANS measures with Table 2) than non-survivors’ autonomic measures. As presented in Figure 2, this is not always the case.

The data in Fig. 2 and Table 3 are from sample patients. The non-survivor data present in the normal (stable) range (compare ANS measures with Table 2), but shows sympathetic (Lfa) and parasympathetic (Rfa) oscillations throughout. The survivor data shows only one peak as an autonomic excursion into marked abnormal ranges then a normalization. The survivors had fluid therapy and a transfusion to correct dehydration and anemia.

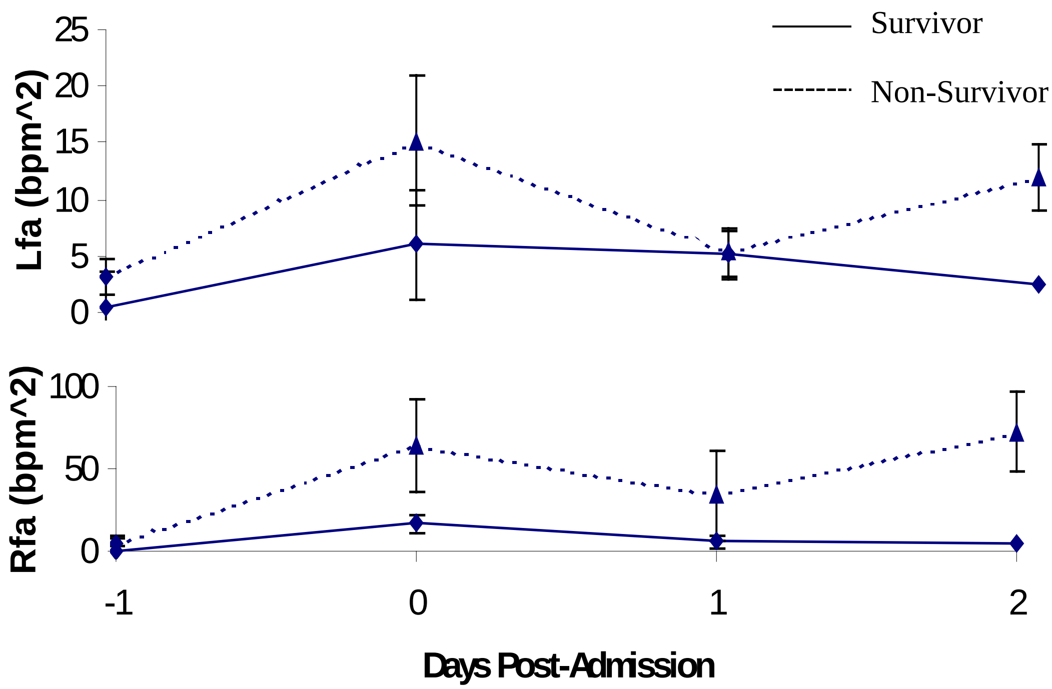

FIGURE 1. Average sympathetic (Lfa) and parasympathetic (Rfa) data from entire cohort plotted as days post-emergency room admission.

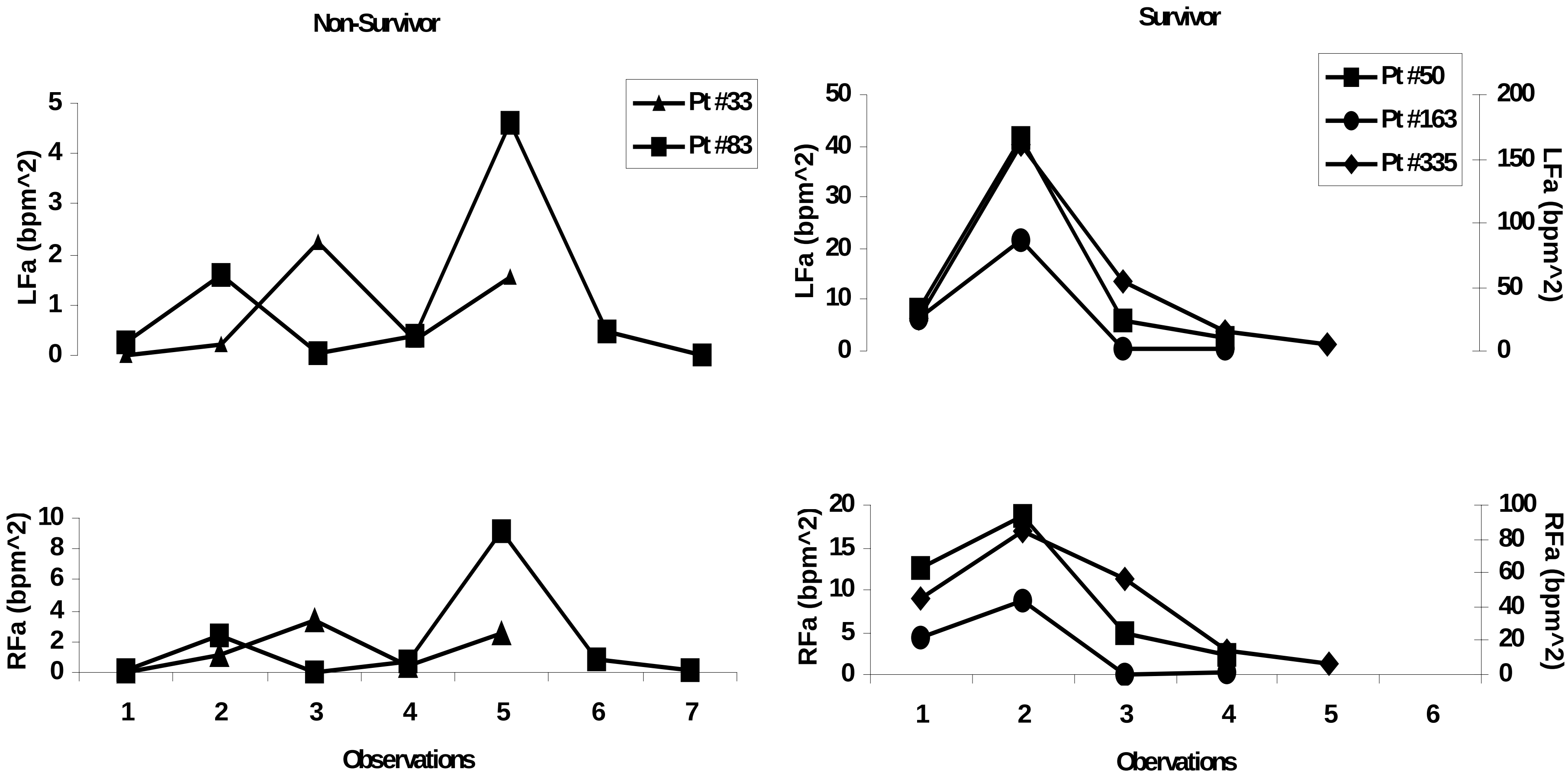

FIGURE 2. Early sympathetic (Lfa) and parasympathetic (Rfa) data from sample non-surviving and surviving septic patients plotted against data sampling time (observations) during the first 48 hours post emergency room admission.

TABLE 2: Salient Clinical Features of the sample patients.

Patient #	S/NS	Age	Gender	ISS	EBL	BSA	GCS
33*	NS	56	F			1.5	
83	NS	57	M	66	5000	2.4	11
50	S	75	F	36	2000	1.9	14
163	S	33	F	26	1500	1.9	12
335	S	30	F	19	400	1.9	9

*Patient 33 is an emergency surgery patient ISS, EBL, and GCS data are not available.
S=survivor, NS=non-survivor, ISS=Injury Severity Score, EBL=estimated blood loss, BSA=body surface area, GCS-Glasgow Coma Score

TABLE 3: Average Hemodynamic data from the sample patients.

Patient #	S/NS	CIbi (Ω)	HR (bpm)	MAP (mmHg)
33	NS	**4.8**±0.87	**89.6**±2.15	**70.3**±6.37
83	NS	**5.5**±1.33	**107.7**±9.64	**64.5**±11.72
50	S	**3.2**±0.29	**78.6**±7.45	**82.9**±6.00
163	S	**4.3**±0.20	**125.3**±4.80	**98.2**±11.08
335	S	**3.7**±0.50	**114.8**±9.69	**96.2**±4.19
		$SapO_2$ (%)	**$PtcCO_2$ (%)**	**$PtcO_2/FiO_2$**
33	NS	**98.8**±0.83	**49.3**±3.20	**220.0**±14.69
83	NS	**97.2**±1.64	**34.9**±6.06	**111.8**±23.16
50	S	**99.2**±0.62	**28.5**±8.37	**195.8**±34.35
163	S	**100**	**51.4**±4.61	**287.9**±50.25
335	S	**97.6**±4.34	**36.7**±2.70	**223.8**±52.66

On average non-survivors had higher ISS indices, higher estimated blood loss (EBL), similar BSA indices, and lower GCS indices. Non-survivors had higher cardiac index (CI), lower heart rates (HR), similar mean arterial pressures (MAP), and similar saturation ($SapO_2$, $PtcO_2/FiO_2$) and perfusion ($PtcO_2/FiO_2$) indices. The details of these patients' hemodynamic patterns in the early ER visit are presented in Figures 3 through 7. The non-surviving patients presented with poor tissue perfusion and oxygenation as indicated by elevated or rising $PtcCO_2$ and low or falling $PtcO_2$. These patients also present with unstable CI, MAP or HR. The surviving patients presented with improving tissue perfusion/oxygenation as indicated by rising $PtcO_2/FiO_2$. These patients also present with stable hemodynamics (CI, MAP, and HR).

Patients with improved or restored ANS early in their ED stay, all survived; while the latter admission to ED had mixed results. ANS balance was not well-correlated with HR, BP, and CI.

CONCLUSION

Sudden surges in SNS and PSNS parameters (Lfa, Rfa, and L/R ratio) preceded the hemodynamic changes that were associated with survival. Reduction in these parameters were associated hemodynamic deterioration, organ failures and death.

Overall the cohort, severe sepsis and septic shock in nonsurvivors was associated with pronounced ANS imbalance (abnormal sympathetic, Lfa, and parasympathetic, Rfa, measures) and instability. Surviving septic patients presented with more normal ANS measures and stability. Septic patients that presented with early abnormal ANS measures, which through intervention was normalized and stabilized, survived. Septic patients who presented with normal ANS measures, though they were not stable did not survive. It is known that poor ANS measures tend to lead to poor outcomes and that normal ANS measures tend to lead to acceptable outcomes. These data support the hypothesis that improved ANS measures lead to improved hemodynamics and favorable outcomes. Average data from all 208 patients indicates that those patients for whom their parasympathetic measure, RFa, drops below 20 within 72 hours survived.

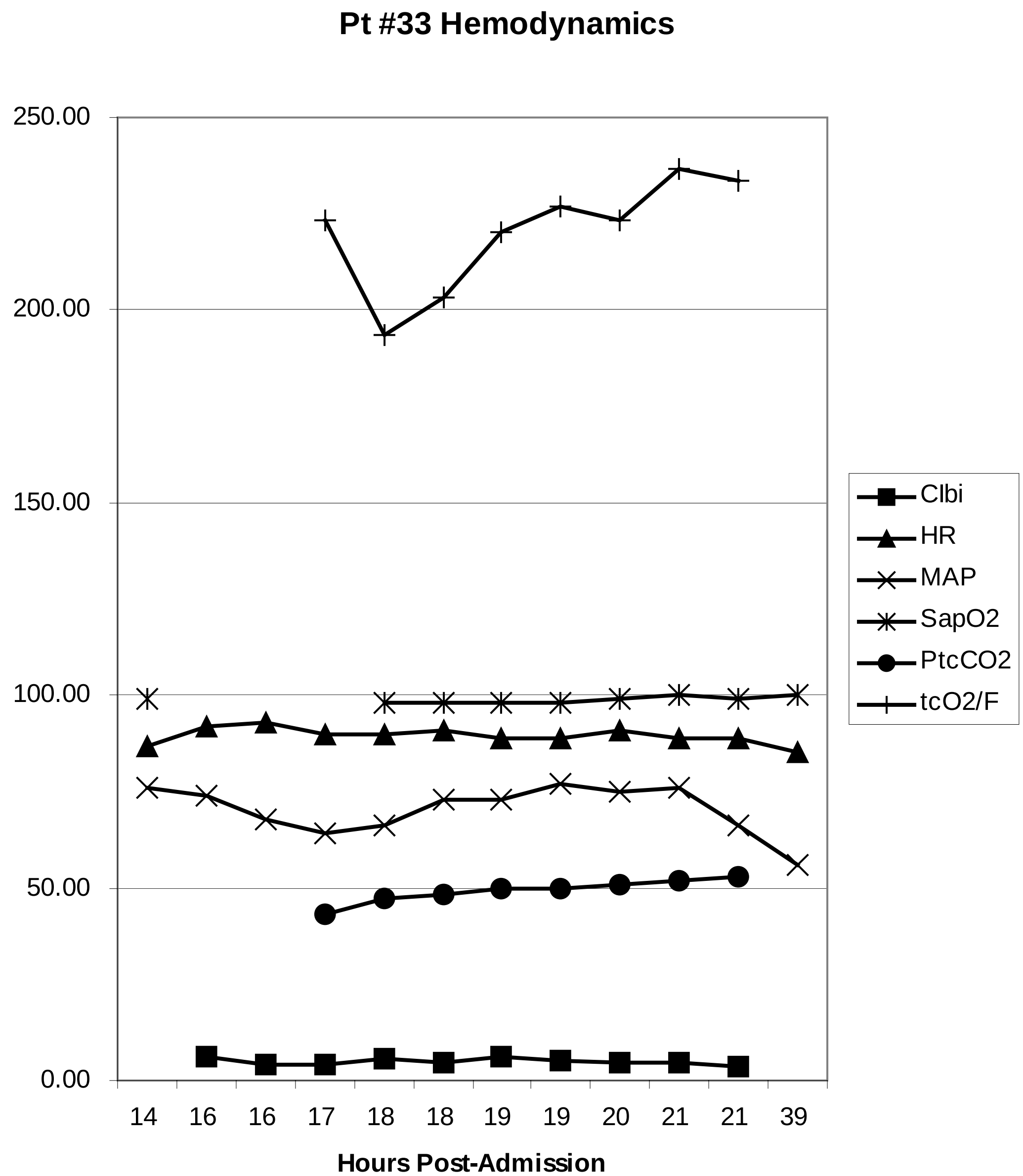

Figure 3: Early hemodynamic patterns for Patient #33, a non-survivor. Note the elevation of $PtcCO_2$ and the fall in $PtcO_2$, indicating poor tissue perfusion and oxygenation. There is a final fall in CI and blood pressure. "tcO2/F" is our abbreviation for $PtcO_2/FiO_2$.

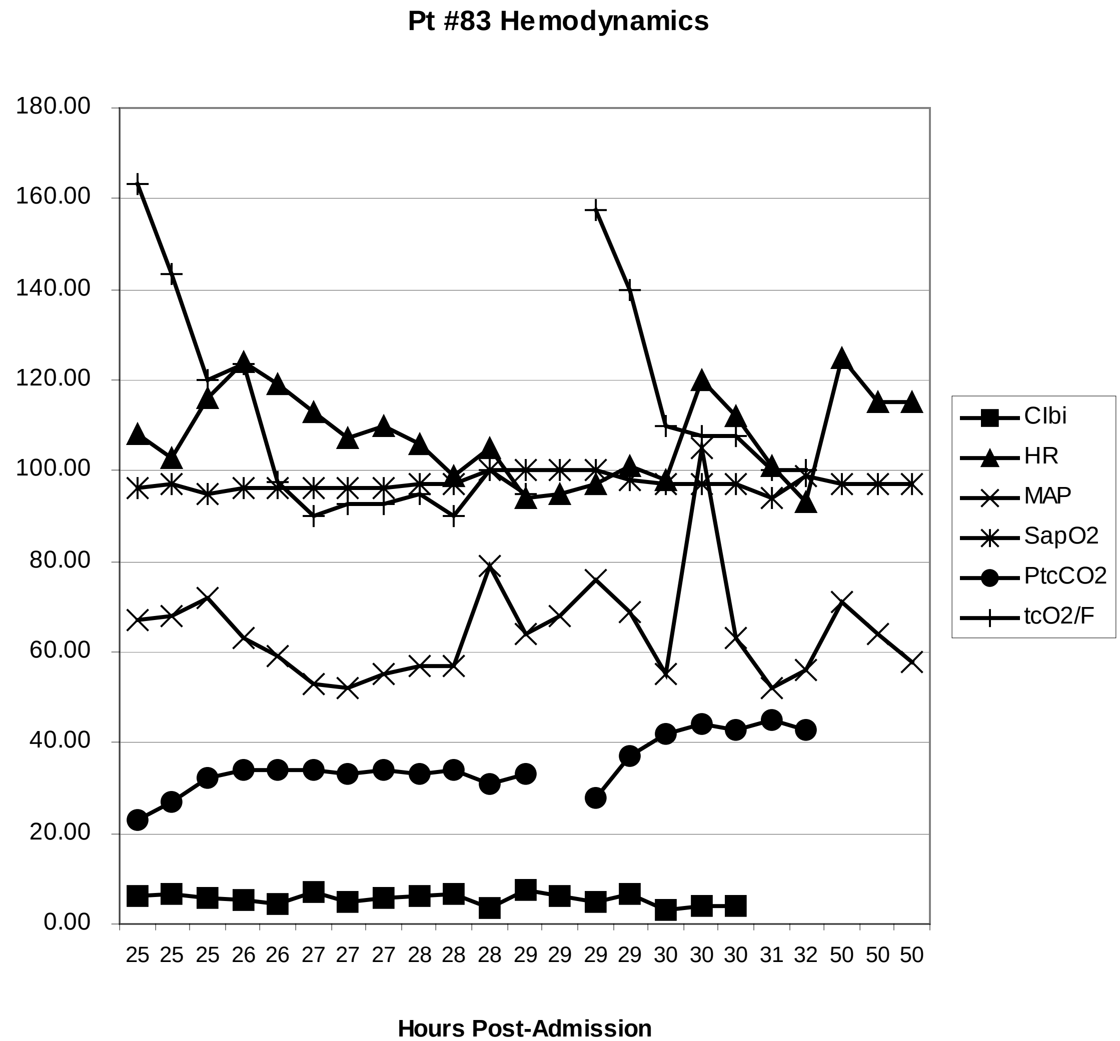

Figure 4: Early hemodynamic patterns for Patient #83, a non-survivor. Note the initial hypertension, tachycardia, the low $PtcO_2$ and rising $PtcCO_2$. The latter indicate poor tissue perfusion/oxygenation. "tcO2/F" is our abbreviation for $PtcO_2/FiO_2$

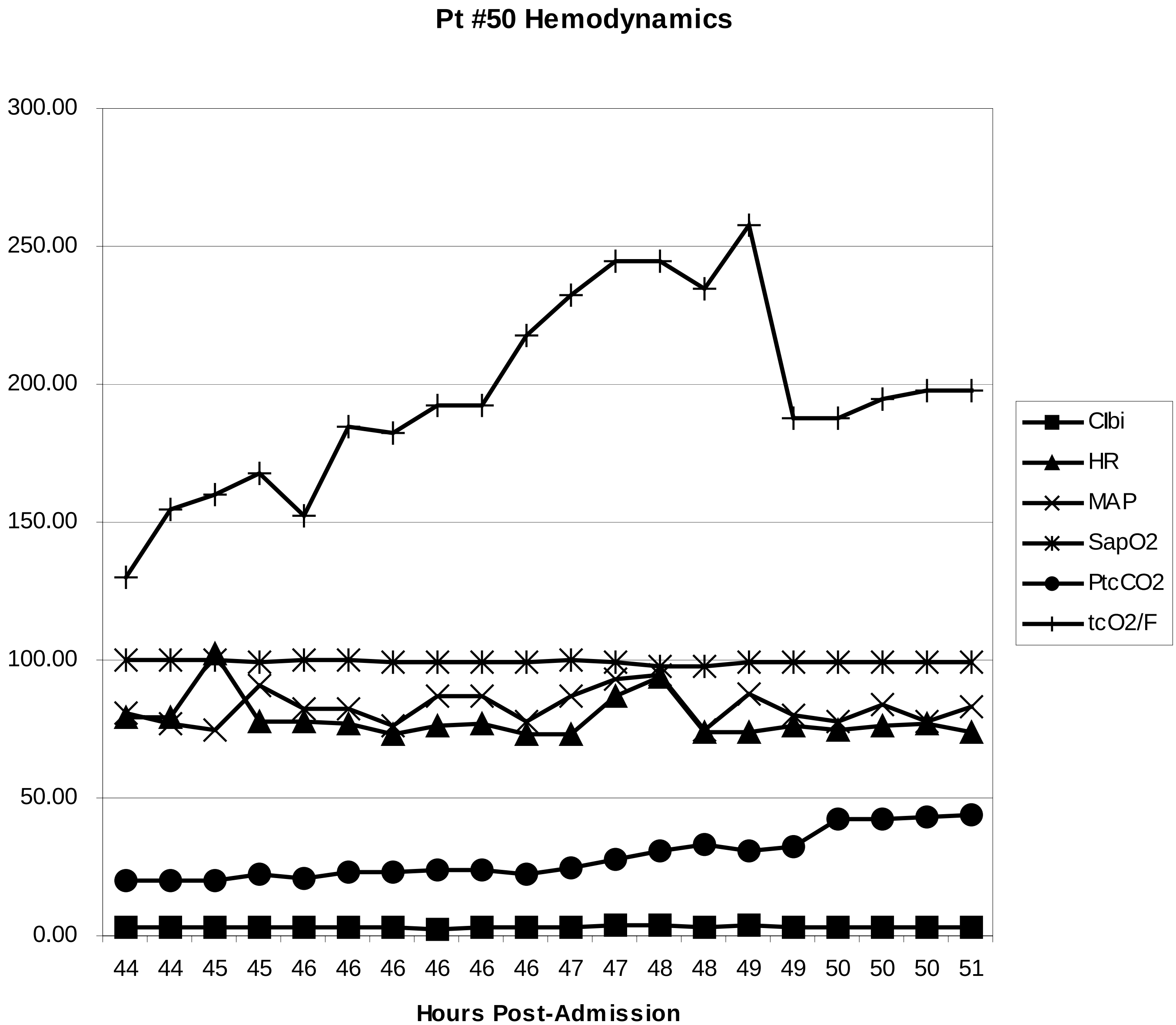

Figure 5: Early hemodynamic pattern for Patient #50, a survivor. Note: the stable CI, MAP, HR, and rising $PtcO_2/FiO_2$ indicating improving tissue perfusion. "tcO2/F" is our abbreviation for $PtcO_2/FiO_2$

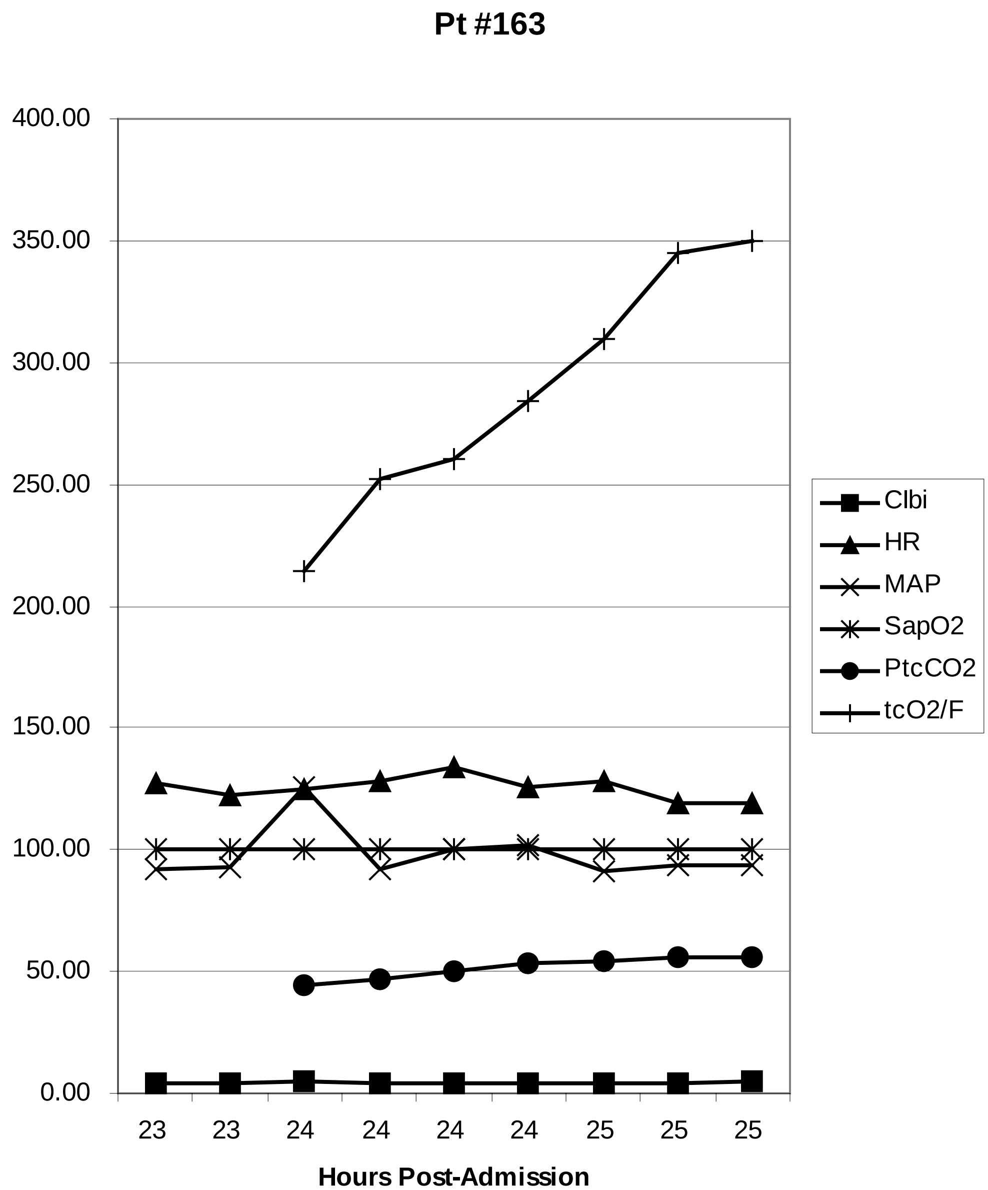

Figure 6: Early hemodynamic patterns for Patient #163, a survivor. Note normal and stable hemodynamics with rising $PtcO_2/FiO_2$ indicating improving tissue perfusion and oxygenation. "tcO2/F" is our abbreviation for $PtcO_2/FiO_2$

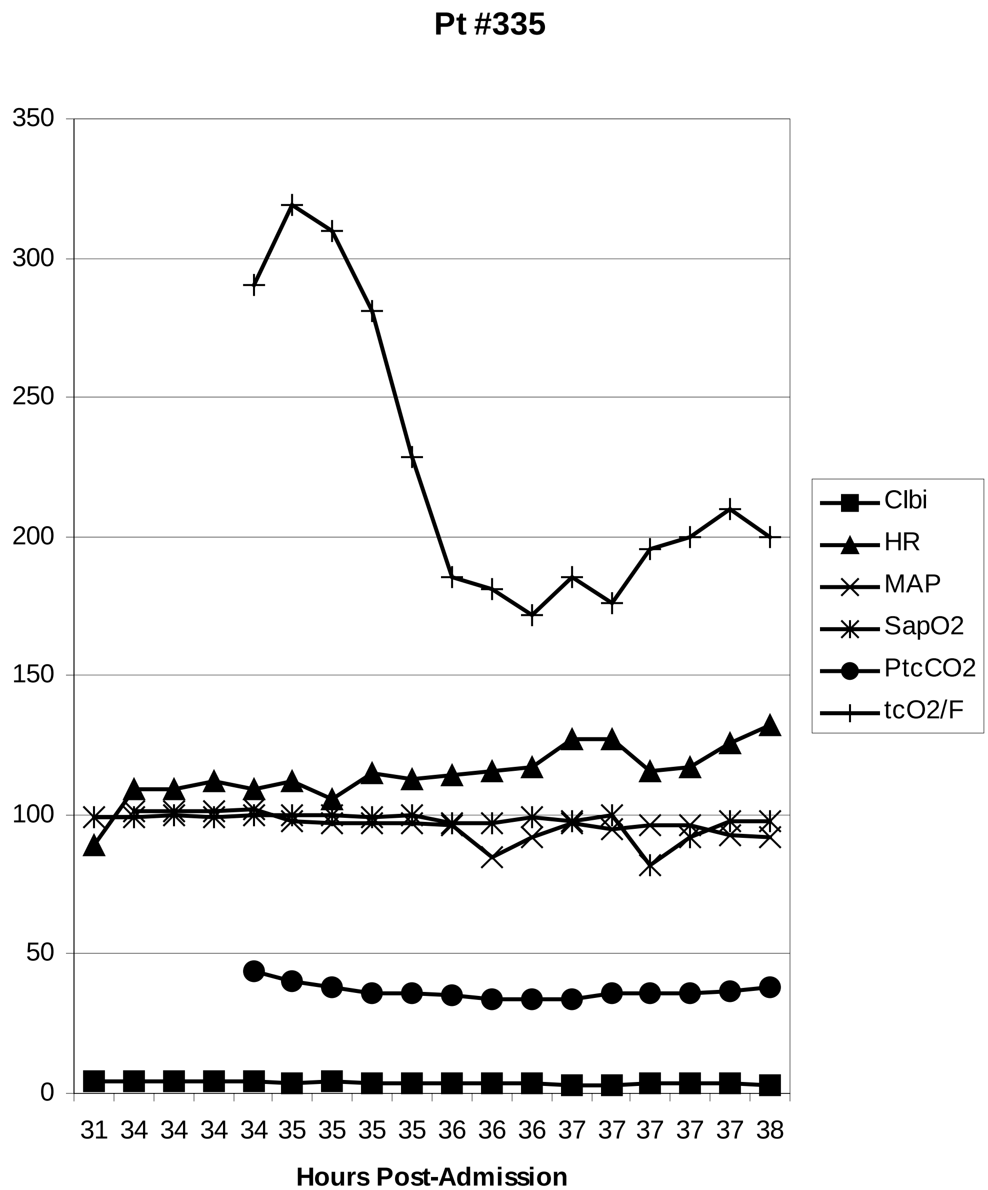

Figure 7: Early hemodynamic patterns for Patient #335, a survivor. Note stable hemodynamics and adequate tissue perfusion/oxygenation. "tcO2/F" is our abbreviation for $PtcO_2/FiO_2$

References

Fathizadeh P, Shoemaker WC, Woo CCJ, and Colombo J: (2004) Autonomic activity in trauma patients based on variability of heart rate and respiratory rate. 2004, Crit Care Med. 32(5), 1300-5.

Dutton R, Shoemaker WC, Blood C, Woo C, and Colombo J. (2001) Examination of real-time heart rate variability during active hemorrhage. Navy Report, NHRC, San Diego, CA.

Zaglaniczny K, Shoemaker WC, Gorguze DS, Woo C, Colombo J, and Blood CG. (2000) An examination of real-time heart rate variability during laparoscopic cholecystectomies and radical surgeries. Navy Report No. 00-47, NHRC, San Diego, CA.