

Prehospital Loss of R-to-R Interval Complexity is Associated With Mortality in Trauma Patients

Andriy I. Batchinsky, MD, Leopoldo C. Cancio, MD, Jose Salinas, PhD, Tom Kuusela, PhD, William H. Cooke, PhD, Jing Jing Wang, MS, Marla Boehme, BS, Victor A. Convertino, PhD, and John B. Holcomb, MD

Background: To improve our ability to identify physiologic deterioration caused by critical injury, we applied nonlinear analysis to the R-to-R interval (RRI) of the electrocardiogram of prehospital trauma patients.

Methods: Ectopy-free, 800-beat sections of electrocardiogram from 31 patients were identified. Twenty patients survived (S) and 11 died (NonS) after hospital admission. Demographic data, heart rate, blood pressure, field Glasgow Coma Scale (GCS) score, and survival times were recorded. RRI complexity was assessed via nonlinear statistics, which quantify entropy or fractal properties.

Results: Age and field heart rate and blood pressure were not different between groups. Mean survival time (NonS) was 129 hours \pm 62 hours. NonS had a lower GCS score (8.6 ± 1.7 vs. 13.2 ± 0.8 , $p < 0.05$). RRI approximate entropy (ApEn; 0.87 ± 0.06 vs. 1.09 ± 0.07 , $p < 0.01$), sample entropy (SampEn; 0.80 ± 0.08 vs. 1.10 ± 0.05 , $p < 0.01$) and fractal dimension by dispersion analysis (1.08 ± 0.02 vs. 1.13 ± 0.01 , $p < 0.05$) were lower in NonS. Distribution of symbol 2 (Dis₂), a symbol-dynamics measure of RRI distribution, was higher in NonS (292.6 ± 34.4 vs. 222 ± 21.3 , $p < 0.10$). For RRI data, logistic regression analysis revealed ApEn and Dis₂ as indepen-

dent predictors of mortality (area under the receiver-operating characteristic curve = 0.96). When GCS_{MOTOR} was considered, it replaced Dis₂ whereas ApEn was retained (area under curve = 0.92). When Injury Severity Score was considered, it replaced GCS_{MOTOR}; ApEn was retained.

Conclusions: Prehospital loss of RRI complexity, as evidenced by decreased entropy, was associated with mortality in trauma patients independent of GCS score or Injury Severity Score.

Key Words: Trauma, Prehospital, Mortality, Electrocardiography, Complexity, Nonlinear analysis, Spectrum analysis.

J Trauma. 2007;63:512–518.

Remote triage, or the early categorization from a distance of patients according to injury severity, may enable decision support and increase situational awareness on the future battlefield. Conventional vital signs such as heart rate and blood pressure, however, are not ideal for this purpose as they have limited predictive accuracy. Thus, improvement in prehospital triage will require new analytical approaches.¹

To generate new, more informative vital signs, analysis of the electrocardiogram (ECG) has been pursued using a variety of techniques. One of these techniques (spectral analysis) measures the strength of periodic oscillations in the heart rate. Heart-rate variability (HRV), that is, variability in the length of the R-to-R interval (RRI) of the ECG, is affected by autonomic nervous system activity.^{2–4} RRI oscillations in the high-frequency range (those occurring at the respiratory rate, known as respiratory sinus arrhythmia) reflect vagal heart-rate control. RRI oscillations at the low-frequency range (about once every 10 seconds) reflect both vagal and sympathetic control of the heart rate. By taking the ratio of the low-frequency-to-high-frequency powers of these oscillations, a measure of the balance between sympathetic and vagal cardiac activities can be obtained (“sympathovagal balance”).³ As one would expect, hypovolemia has been shown to cause a compensatory increase in sympathovagal balance.^{5–7} On the other hand, sympathetic failure, manifested by a decrease in sympathovagal balance, was predictive of death in intensive care unit patients^{8,9} and in prehospital trauma patients.^{10,11}

Rather than measure the strength of the periodic oscillations in the heart rate, an alternative approach to analysis of RRI variability measures the amount of irregularity, or complexity, in the heart rate. This irregularity is the result of the intricate and multilayered control mechanisms that fine-tune the heart rate.¹² Complexity is a feature of normal cardiovascular regulation, whereas loss of complexity or “decomplexi-

Submitted for publication December 8, 2006.

Accepted for publication June 15, 2007.

Copyright © 2007 by Lippincott Williams & Wilkins

From the US Army Institute of Surgical Research (A.I.B., L.C.C., J.S., J.J.W., M.B., V.A.C., J.B.H.), Fort Sam Houston, Texas; Department of Physics (T.K.), University of Turku, Turku, Finland; and Laboratory for Applied Autonomic Neurophysiology, Department of Health and Kinesiology (W.H.C.), University of Texas, San Antonio, Texas.

Supported by the Combat Critical Care Engineering Program, US Army Medical Research and Materiel Command, Fort Detrick, Maryland.

The work was conducted at the US Army Institute of Surgical Research.

The opinions or assertions contained herein are the private views of the authors, and are not to be construed as official or as reflecting the views of the Department of the Army or the Department of Defense.

Presented as a poster at the 20th Annual Meeting of the Eastern Association for the Surgery of Trauma, January 16–20, 2007, Fort Meyers, Florida.

Address for reprints: Andriy I. Batchinsky, MD, US Army Institute of Surgical Research, 3400 Rawley E. Chambers Avenue, Fort Sam Houston, Texas 78234-6315; email: andriy.batchinsky@amedd.army.mil.

DOI: 10.1097/TA.0b013e318142d2f0

Report Documentation Page

Form Approved
OMB No. 0704-0188

Public reporting burden for the collection of information is estimated to average 1 hour per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Washington Headquarters Services, Directorate for Information Operations and Reports, 1215 Jefferson Davis Highway, Suite 1204, Arlington VA 22202-4302. Respondents should be aware that notwithstanding any other provision of law, no person shall be subject to a penalty for failing to comply with a collection of information if it does not display a currently valid OMB control number.

1. REPORT DATE 01 SEP 2007		2. REPORT TYPE N/A		3. DATES COVERED -	
4. TITLE AND SUBTITLE Prehospital loss of R-to-R interval complexity is associated with mortality in trauma patients				5a. CONTRACT NUMBER	
				5b. GRANT NUMBER	
				5c. PROGRAM ELEMENT NUMBER	
6. AUTHOR(S) Batchinsky A. I., Cancio L. C., Salinas J., Kuusela T., Cooke W. H., Wang J. J., Boehme M., Convertino V. A., Holcomb J. B.,				5d. PROJECT NUMBER	
				5e. TASK NUMBER	
				5f. WORK UNIT NUMBER	
7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES) United States Army Institute of Surgical Research, JBSA Fort Sam Houston, TX 78234				8. PERFORMING ORGANIZATION REPORT NUMBER	
9. SPONSORING/MONITORING AGENCY NAME(S) AND ADDRESS(ES)				10. SPONSOR/MONITOR'S ACRONYM(S)	
				11. SPONSOR/MONITOR'S REPORT NUMBER(S)	
12. DISTRIBUTION/AVAILABILITY STATEMENT Approved for public release, distribution unlimited					
13. SUPPLEMENTARY NOTES					
14. ABSTRACT					
15. SUBJECT TERMS					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT SAR	18. NUMBER OF PAGES 7	19a. NAME OF RESPONSIBLE PERSON
a. REPORT unclassified	b. ABSTRACT unclassified	c. THIS PAGE unclassified			

fication” of the RRI has been shown in several studies to be a feature of disease¹³ and of impaired adaptation to physiologic stress.¹⁴

In this article, we use the term “complexity analysis” to refer to a family of tools more properly termed nonlinear statistics. Nonlinear behavior is the rule in biology. Biologic processes cannot be described by analysis of the simple sums of component variables, but involve products and powers of these constantly interacting variables. In the cardiovascular system, one consequence of this nonlinearity is the complex irregularity of the RRI. Nonlinear statistics are well suited for analysis of such signals.

We previously found in two animal models of hemorrhagic shock that RRI complexity, as measured by the Approximate Entropy technique, decreases during shock and is restored by fluid resuscitation.^{15,16} Similarly, others documented a decrease in the complexity of the RRI in human volunteers subjected to central hypovolemia by means of lower body negative pressure.¹⁷ The objective of the present study was to evaluate the ability of several such methods to discriminate between survivors and nonsurvivors of trauma in the prehospital setting. We hypothesized that loss of RRI complexity is associated with mortality after trauma.

MATERIALS AND METHODS

The Institutional Review Boards of the University of Texas Health Science Center, Houston, TX, and Brooke Army Medical Center, Fort Sam Houston, TX approved this study.

Patients were identified for this study using the Trauma Vitals database developed by the US Army Institute of Surgical Research (Fort Sam Houston, TX).¹ The database stores prehospital patient data from point of injury until delivery via Life Flight helicopter to Memorial Hermann Hospital, a regional Level I trauma center in Houston, TX.

A ProPaq 206EL vital signs monitor (WelchAllyn, Skaneateles Falls, NY) and a standard run sheet were used for data collection. Continuous ECG waveforms were collected with an iPAQ (Talla-tech RPDA, Tallahassee, FL) personal digital assistant interfaced to the monitor, and were recorded at a sampling frequency of 182 Hz. Vital signs, mechanism of injury (MOI, blunt or penetrating), field Glasgow Coma Scale (GCS) score, Abbreviated Injury Scores, Injury Severity Score (ISS), age, sex, and demographics were recorded. Blood pressures were measured automatically by cuff using the vital signs monitor. Blood pressures presented in this report were taken from the time point closest to the ECG segment extracted for analysis.

Patient Selection

The available data (117 patients recorded using the ProPaq 206EL vital signs monitor) were screened for presence of ECG recordings free of electromechanical noise (severe enough to prevent R-wave identification), free of ectopic beats, and at least 800 heart beats in length. Thirty-one

patients with ectopy-free ECG waveforms were selected according to the above criteria from the 117 candidates available. Eighty-six patients were excluded because of multiple ectopic beats in the time series ($S = 34$, $NonS = 13$); electromechanical noise ($S = 10$, $NonS = 22$); or inadequate data length ($S = 5$, $NonS = 2$).

ECG Analysis

Eight-hundred-beat data sets from each subject were imported into WinCPRS software (Absolute Aliens Oy, Turku, Finland) and analyzed as a single discrete dataset as previously described.^{15,18} Eight-hundred beats were selected because HRV statistics are affected by the number of data points. Automatic identification of R waves was performed by the software, and manually verified in every data set. The software generated the instantaneous RRI time series.

The following are the main variables that were calculated:

Time-Domain Analyses⁴

1. Mean RRI: the mean of the RRI, measured in milliseconds.
2. RMSSD: the square root of the mean of the sum of the squares of differences between consecutive RRIs.
3. pNN50: percentage of intervals that vary more than 50 ms from the previous interval.

Spectral Analysis (Fast Fourier Transform)

1. Low-frequency component of the RRI power spectrum, or low-frequency (LF) power: influenced by both sympathetic and vagal activity.
2. High-frequency (HF) power: influenced by vagal activity.
3. LF/HF and HF/LF ratios: reflect sympathovagal balance.
4. Total power: reflects the strength of oscillations throughout the entire power spectrum.
5. The LF, HF, and LF/HF ratio were normalized by dividing the LF and HF spectra by the total power. This yielded normalized powers (LF_{nu} , HF_{nu}) and their ratios (LF_{nu}/HF_{nu} , HF_{nu}/LF_{nu}).

Spectral Analysis (Complex Demodulation)

The method of complex demodulation (CDM) provides continuous assessment of the amplitude of high- and low-frequency fluctuations in the RRI.¹⁹

1. CDM LF: a measure of the amplitude of the low-frequency fluctuations in the RRI.
2. CDM HF: a measure of the amplitude of the high-frequency fluctuations in the RRI.

Complexity Analysis (Nonlinear Statistics)

1. Approximate entropy (ApEn)²⁰ and sample entropy (SampEn)²¹: measure the amount of irregularity in the RRI signal.
2. Fractal dimension by dispersion analysis (FDDA) and fractal dimension by curve lengths (FDCL): determine the fractal organization of the signal.¹⁸

3. Detrended fluctuations analysis (DFA): determines fractal-like correlation properties and uncovers short- and long-range correlations within the signal.²²
4. Similarity of distributions (SOD): explores the probability of similar RRI signal-amplitude distributions as a function of time.²³
5. Signal stationarity (StatAv): assesses whether the mean and SD of the signal change during time during each data set.²⁴
6. Symbol dynamics indices: symbol dynamics entropy (SymDyn), percentage of forbidden words (FW), and normalized symbol dynamics entropy (DisnEn) collectively measure the probability of certain patterns within the RRI time series.²⁵

Statistical Analysis

SAS version 8.1 (SAS Institute, Cary, NC) was used. Univariate analysis was performed using two-sample Student's *t* test or Wilcoxon's ranked sum test as appropriate for continuous variables, and the Cochran-Mantel-Haenszel statistic for score variables. In addition, correlation coefficients were calculated to determine relationships between continuous variables (Pearson correlation) and between dichotomous and continuous variables (point-biserial correlation). Spearman correlations were calculated between ordinal and continuous variables.

Multiple logistic regressions with stepwise selection and likelihood ratio tests were performed to identify independent predictors of mortality. Candidate variables were ECG-derived metrics as well as the motor component of the field GCS (GCS_{MOTOR}) and the ISS. In the construction of logistic regression models to predict mortality, we considered this to represent a diagnostic problem with three overlapping phases. In the first phase ("remote triage"), only data derived from the RRI, and thus potentially available by remote telemetry, were considered. In the second phase ("prehospital care"), additional data available to the field medic, to include the GCS_{MOTOR}, were also considered. In the third and final phase ("definitive care"), data available during hospitalization, including the ISS, were also considered.

We chose variables with a *p* value of <0.2 by univariate analysis as candidates for the logistic models. The Hosmer-Lemeshow goodness-of-fit test was used to estimate the regression model fit. A receiver-operating characteristic curve was constructed to assess the diagnostic performance of predictive equations. Estimated odds ratios and their 95% confidence intervals (CIs) were determined by the maximum likelihood method. The change in the Pearson χ^2 statistic caused by deleting an individual observation was used to detect ill-fitted observations or outliers. If the model excluding outliers and influential cases had a classification accuracy rate that was better than the baseline model, which included all cases, the revised model was used. If the accuracy rate of

the revised model without outliers and influential cases was less than 2% more accurate, the baseline model was retained.

RESULTS

Age and hemodynamic data, to include the heart rate, were not statistically different between nonsurvivors (NonS) and survivors (S) (Table 1). Male gender and blunt mechanism of injury were relatively more common in the S group than in the NonS group. NonS were more severely injured and had a significantly lower GCS_{TOTAL} and GCS_{MOTOR}, and a higher ISS and Abbreviated Injury Score for the head (Table 1). Mean survival time (NonS) was 129 hours \pm 62 hours.

Time-domain and spectral analysis results are shown in Table 2. CDM revealed the amplitude of the LF oscillations of the RRI (significantly) and the HF oscillations of the RRI (not significantly) to be lower in NonS (Table 2). We additionally observed the following trends (not significant). NonS had lower nonnormalized HF and higher HF_{nu} than the S group. The LF, LF_{nu}, as well as LF/HF and LF_{nu}/HF_{nu} ratios were lower in NonS.

Complexity measures (obtained by nonlinear statistics) (Table 3), to include ApEn, SampEn, FDDA and the short-term scaling exponent by DFA were statistically (*p* < 0.05) lower in NonS than in S. Lower FDCL, Lempel-Ziv entropy (LZEn), and spectral entropy (SpEn) in NonS were not statistically distinguishable from S (data not shown). SOD was higher in NonS. StatAv was not different between the groups (Table 3).

Distribution of symbol 6 (Dis₆), a symbol dynamics measure of RRI complexity, was lower in NonS (273.55 \pm 27.99 vs. 336.60 \pm 16.54, *p* < 0.05). Distribution of symbol 2 (Dis₂), was higher in NonS (292.6 \pm 34.4 vs. 222 \pm 21.3, *p* = 0.08). Other symbol distributions were not different between groups

Table 1 Demographics, Conventional Vital Signs, and Injury Scores

Variable	NonS	S
Age (yr)	43.36 \pm 5.79	38.10 \pm 3.40
Sex	M (7), F (4)	M (15), F (5)
MOI	B (6), P (5)	B (13), P (7)
HR	117.46 \pm 8.54	99.63 \pm 4.39
MAP	74.62 \pm 9.54	82.7 \pm 4.84
GCS _{TOTAL}	8.64 \pm 1.70*	13.17 \pm 0.82
GCS _{MOTOR}	3.36 \pm 0.72†	5.50 \pm 0.32
AISS _{HEAD}	3.00 \pm 0.73*	0.70 \pm 0.34
ISS	36.55 \pm 2.90‡	12.40 \pm 1.97

Data are means \pm SEM.

**p* < 0.05.

†*p* < 0.01.

‡*p* < 0.001.

NonS, nonsurvivors; S, survivors; MOI, mechanism of injury; B, blunt; P, penetrating; MAP, mean arterial pressure; HR, heart rate; GCS_{TOTAL}, field Glasgow Coma Score total; GCS_{MOTOR}, field Glasgow Coma Score motor; AISS_{HEAD}, Abbreviated Injury Score for the head; ISS, Injury Severity Score.

Table 2 Time- and Frequency-Domain Analysis Results

Variable	NonS	S
RRI	543.91 ± 47.37	626.30 ± 29.47
RMSSD	8.09 ± 2.16	11.60 ± 1.99
pNN50	0.38 ± 0.36	1.22 ± 0.99
TP	1673 ± 1325	576.35 ± 151.55
LF	174.64 ± 75.12	233.00 ± 62.22
HF	44.45 ± 17.83	73.05 ± 26.03
LF/HF	481.01 ± 201.53	558.12 ± 175.65
HF/LF	0.73 ± 0.23	0.34 ± 0.05
LF _{nu}	0.57 ± 0.09	0.74 ± 0.03
HF _{nu}	0.29 ± 0.05	0.22 ± 0.02
LF _{nu} /HF _{nu}	4.81 ± 2.01	5.55 ± 1.73
HF _{nu} /LF _{nu}	0.67 ± 0.20	0.33 ± 0.04
CDM LF	9.09 ± 4.15*	13.10 ± 2.11
CDM HF	3.27 ± 1.05	6.15 ± 1.24

Data are means ± SEM.

* *p* < 0.05.

NonS, non-survivors; S, survivors; RRI, mean R-to-R interval of the ECG; RMSSD, root mean square standard deviation; pNN50, percentage of R-R intervals that vary by at least 50 ms; TP, total R-to-R interval spectral power (0.003–0.4 Hz ms²); LF, RRI spectral power at the low frequency (0.05–0.15 Hz ms²); HF, RRI spectral power at the high frequency (0.15–0.4 Hz ms²); LF/HF, the nonnormalized ratio of LF to HF; HF/LF, the nonnormalized ratio of HF to LF; LF_{nu} and HF_{nu}, LF and HF spectral powers normalized to total power; LF_{nu}/HF_{nu}, ratio of LF_{nu} to HF_{nu}; HF_{nu}/LF_{nu}, ratio of HF_{nu} to LF_{nu}; CDM LF, amplitude of the LF oscillations; CDM HF, amplitude of the HF oscillations.

Table 3 Nonlinear Analysis Results

Variable	NonS	S
ApEn	0.87 ± 0.06*	1.09 ± 0.04
SampEn	0.80 ± 0.08*	1.10 ± 0.05
FDDA	1.08 ± 0.02 [†]	1.13 ± 0.01
DFA	0.93 ± 0.14 [†]	1.26 ± 0.08
SOD	0.28 ± 0.04 [†]	0.19 ± 0.02
StatAv	0.89 ± 0.05	0.82 ± 0.03
FW (%)	51.45 ± 4.91	52.55 ± 2.28
DisnEn	0.62 ± 0.04	0.65 ± 0.02

Data are means ± SEM.

* *p* < 0.01.

[†] *p* < 0.05.

ApEn, approximate entropy; SampEn, sample entropy; FDDA, fractal dimension by dispersion analysis; DFA, detrended fluctuations analysis; SOD, similarity of distributions; StatAv, stationarity; FW, percentage of forbidden words; DisnEn, normalized symbol-dynamics entropy.

(data not shown). FW were not different and the normalized entropy of the symbol dynamics (DisnEn) showed lower numerical values (N.S.) for the NonS (Table 3).

Association With Mortality

As explained above, construction of logistic regression models for prediction of mortality progressed through three phases. For the remote triage phase, RRI data were considered. ApEn and SampEn were highly correlated with each

other (*r* = 0.99), and we selected ApEn for inclusion into our predictive models. Out of all the ECG-calculated variables, two independent predictors of mortality were identified: ApEn and Dis_2. The predictive model based on these variables produced the following equation:

$$P(\text{mortality}) = e^k / (1 - e^k), \text{ where}$$

$$k = 4.29 - 7.33 * (\text{ApEn}) + 0.0092 * (\text{Dis}_2).$$

The area under the receiver-operating characteristic curve (AUC) = 0.86 (95% CI = 0.71–1.0). After exclusion of outliers (1 case in NonS and 2 in S) the revised model improved:

$$P(\text{mortality}) = e^k / (1 - e^k), \text{ where}$$

$$k = 9.91 - 14.78 * (\text{ApEn}) + 0.02 * (\text{Dis}_2).$$

$$\text{AUC} = 0.956, (95\% \text{ CI} = 0.86\text{--}1.0; \text{ Fig. 1}).$$

For the second or prehospital care phase, GCS_{MOTOR} was added to the model yielding:

$$P(\text{mortality}) = e^k / (1 - e^k), \text{ where } k = 5.46$$

$$- 6.25 * (\text{ApEn}) + 0.01 * (\text{Dis}_2) - 0.41 * (\text{GCS}_{\text{MOTOR}}).$$

AUC = 0.886 (95% CI = 0.75–1.0). After exclusion of outliers (1 case in group S) Dis_2 was excluded from the model, whereas ApEn was retained:

$$P(\text{mortality}) = e^k / (1 - e^k), \text{ where}$$

$$k = 14.95 - 10.92 * (\text{ApEn}) - 0.87 * (\text{GCS}_{\text{MOTOR}}).$$

$$\text{AUC} = 0.92 (95\% \text{ CI} = 0.80\text{--}1.0; \text{ Fig. 2}).$$

Upon consideration of the ISS for the third or definitive care phase, it replaced the GCS_{MOTOR} in the model, whereas ApEn was again retained:

$$P(\text{mortality}) = e^k / (1 - e^k), \text{ where}$$

$$k = -1.11 - 7.29 * (\text{ApEn}) + 0.29 * (\text{ISS}).$$

$$\text{AUC} = 0.977 (95\% \text{ CI} = 0.91\text{--}1.0; \text{ Fig. 3}).$$

For all the above models, the Hosmer and Lemeshow goodness-of-fit test revealed no significant departure from good fit (*p* > 0.2).

DISCUSSION

This report introduces the use of complexity analysis of the RRI for prediction of mortality in prehospital trauma patients. There were two principal findings: (1) prehospital loss of RRI complexity, as measured by several complementary but computationally different nonlinear metrics, characterized and separated nonsurvivors from survivors. (2) One measure of RRI complexity, ApEn, was an independent predictor of in-hospital mortality, even when variables such as field GCS_{MOTOR} and ISS were taken into account. ApEn outperformed traditional vital signs, such as blood pressure and

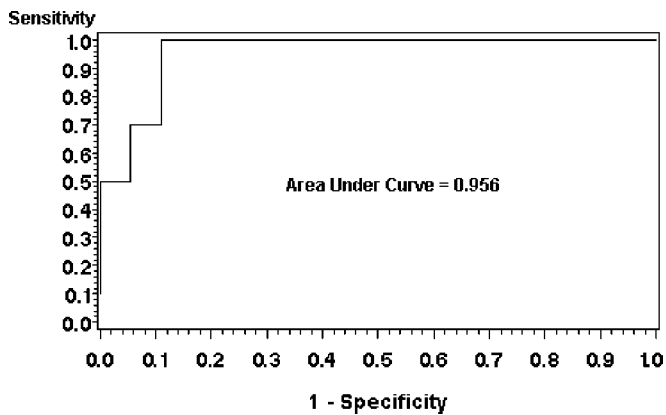


Fig. 1. Receiver-operating characteristic curve of the model based on ECG-derived (ApEn and Dis_2) predictors of mortality (“remote triage” model).

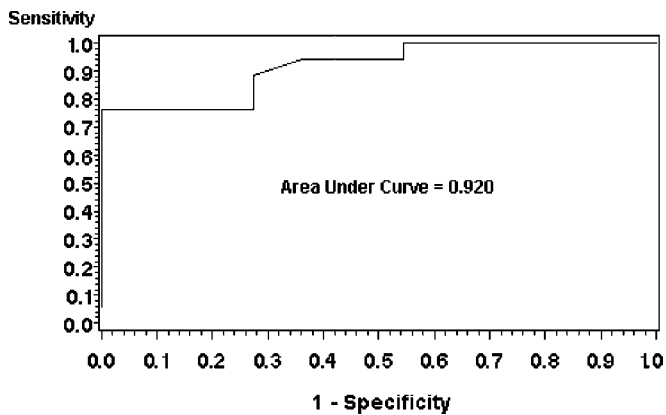


Fig. 2. Receiver-operating characteristic curve of the model based on ApEn and GCS_{MOTOR} (“prehospital care” model).

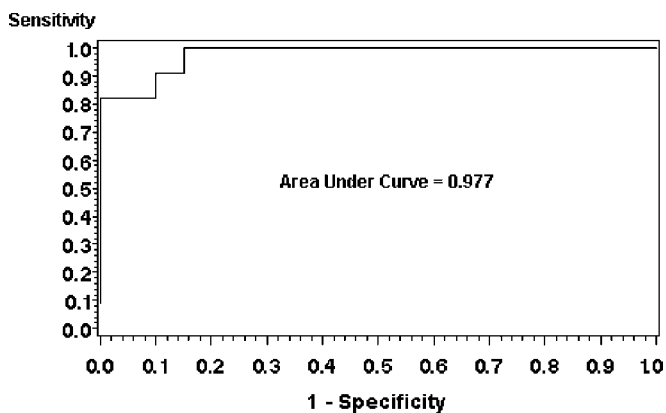


Fig. 3. Receiver-operating characteristic curve of the model based on ApEn and ISS (“definitive care” model).

heart rate, which did not demonstrate statistically significant differences between nonsurvivors and survivors in this study.

Complexity Analysis

Physiologic processes such as the RRI display nonlinear responses to stimuli and feature complex, irregular patterns

of variability.^{26–28} These complex patterns in the signal reflect input from multiple, interacting, feedback-controlled systems.^{26,28,29} We think that analysis of the complexity of the RRI with nonlinear methods allows assessment of the complexity, and thus the health, of the underlying system, which controls the heart rate.^{20,27,29}

Why does RRI complexity exist? Passage of information through nonlinear regulatory networks probably facilitates adaptability to stress,^{14,28} whereas loss of complexity may imply maladaptation and informational isolation of the system.³⁰ This may explain why a system with higher complexity is associated with survival and is more error tolerant,³¹ whereas a system with low complexity and less variability is associated with disease¹³ or death. However, the precise mechanism(s) responsible for the observed changes in complexity with disease or shock remain to be deciphered.

One method of measuring RRI complexity quantifies the amount of irregularity, or entropy, in the signal. In our study, ApEn and SampEn were lower in nonsurvivors than in survivors. Palazzolo et al. documented a decrease in ApEn secondary to hypotension in dogs.³² Similarly, we showed decreased ApEn and SampEn during hemorrhagic shock in anesthetized swine.¹⁵ Hogue et al. identified that decreased entropy was an independent predictor of atrial fibrillation in patients after coronary artery bypass grafting.³³ Decreased entropy was associated with myocardial ischemia, manifested by angina.³⁴ Thus, decreases in RRI complexity as measured by entropy appear to be associated with physiologic deterioration in a variety of conditions.

Another method of measuring RRI complexity takes advantage of the fact that the normal RRI possesses fractal characteristics. This means that shorter sections of the RRI are structurally similar to longer sections, i.e. that the signal possesses “self-similarity” at both small and large scales.³⁵ As measured by FDDA (significantly) and FDCL (nonsignificantly), NonS showed a loss of fractal structure. We have previously shown a decrease in FDDA during hemorrhagic shock in swine.¹⁵ West et al. found a decline in RRI fractal dimension in humans during central hypovolemia induced by lower body negative pressure.¹⁷ A breakdown in fractal properties may be an indicator of a more regular structural organization of the signal and solidifies our findings of lower complexity in the NonS group.

DFA is another method of measuring the self-similarity of fractal processes that quantifies the short- and long-term correlations within the data.²² In this study we assessed the scaling exponent reflecting the short-term correlations in the RRI signal and found it to be significantly lower in the NonS, denoting breakdown of correlations. In 24-hour Holter recordings of 446 survivors of myocardial infarction, Huikuri et al. found the DFA short-term exponent to be an independent predictor of death.³⁶ Loss of RRI complexity measured by decreased short-term fractal scaling properties predicted mortality in survivors of acute myocardial infarction.³⁷ Vikman et al. found that a decrease in RRI ApEn and short-term RRI

dynamics (DFA) preceded the spontaneous onset of atrial fibrillation in patients with no structural heart disease, whereas traditional HRV metrics did not change.³⁸ Our findings are therefore consistent with the literature indicating an association between loss of RRI fractal scaling and life-threatening disease.

SOD is a method that allows for rapid online analysis of small datasets, as it explores the probability of similar RRI signal amplitude distributions as a function of time.²³ SOD was higher in NonS, reflecting greater regularity of signal distribution and thus a state of lower complexity among NonS.

The symbol-dynamic indices collectively measure the probability of certain patterns within the RRI time series.²⁵ In our study, the FW and the normalized entropy of the symbol dynamics (DisEn) were not different between the groups, possibly denoting low sensitivity of this method.³² In addition, we found that the average of pattern 6 of symbol words (Dis_6) was higher and pattern 2 (Dis_2) was lower in NonS, with the latter included into the “remote triage” predictive model. At this point, limited experience with these methods prevents us from drawing firm conclusions about the physiologic meaning of these specific patterns (Dis_6 and Dis_2), and application of the methods to larger data sets will be needed to place these findings in perspective.

Spectral Analysis

The method of CDM provides continuous assessment of the amplitude of high- and low-frequency fluctuations in the RRI, and is insensitive to data length and nonstationarity in the signal.¹⁹ As measured by CDM, the amplitude of LF and HF oscillations (the latter nonsignificantly) were both lower in NonS. These changes paralleled those seen in the standard nonnormalized frequency-domain metrics. Overall, these findings indicate inappropriately low sympathetic activity in the NonS group.

Previous work by Winchell and Hoyt on intensive care unit patients,⁹ as well as from our institution on prehospital trauma patients,^{10,11} identified lack of sympathetic tone and a state of decreased sympathovagal balance in NonS.^{9,10} Consistent with those reports, in this study the trends in the LF, LF_{nu}, and LF/HF ratio were all numerically lower in the NonS group along with a higher HF_{nu}, HF/LF ratio, and HF_{nu}/LF_{nu} ratio (Table 2). Lack of statistical significance in these observations likely reflects sample size, dataset length and, perhaps, the methodologic limitations of these methods.

Prediction of Mortality

The first predictive model explored in our study reflected the discriminative capacity of ECG-derived metrics alone, and modeled a scenario in which an ECG signal is analyzed remotely and before hands-on evaluation of the casualty (“remote triage” model). The respectable sensitivity and specificity (that further improved with elimination of outliers) underlines the potential utility of entropy measurements for

remote prognosis and diagnosis. Inclusion of the GCS_{MOTOR} in the second predictive model conceptualizes arrival of a medic to the casualty and a physical examination in addition to the ECG analysis (“prehospital care” model). Finally, in the third (“definitive care”) model, ApEn was retained and ISS was added as independent predictors of mortality. Thus, in this dataset ApEn possibly accounts for differences in the robustness of an individual’s response to injury, even when ISS is taken into account.

Limitations

The hemodynamic data (heart rate and mean arterial blood pressure) were numerically but not statistically different between S and NonS in this study. Thus, the possibility of a type II error exists in this small sample size. We investigated prehospital trauma patients with ECGs that did not contain prohibitive levels of mechanical noise or arrhythmias, and were 800 beats long. These limitations led us to the sample size of 31 of the original 117 as outlined in our patient inclusion criteria. It is possible that those trauma victims who are more critically ill, and therefore more likely to die, might have more noisy ECGs because of, for example, ongoing interventions during transport. Indeed, the mortality rate was 43% in the excluded group versus 35% in the included group. Otherwise, excluded patients did not differ from included patients with respect to the male-to-female ratio, age, mean arterial pressure, or ISS. Clearly, however, it would be premature to generalize our findings to other trauma patients. Efforts are ongoing to improve the quality of ECG results collected in the field, and to determine the absolute minimum dataset length (number of beats) needed for accurate patient classification. Reduction of dataset size would widen the utility of the proposed methods during short transport times.

The endpoint, in-hospital mortality, was chosen in our study for its unequivocal ability to categorize outcome. However, of greater importance to the prehospital provider is the ability to predict the need for a lifesaving intervention. Studies are ongoing to verify the utility of the methods explored here in prediction of lifesaving interventions.

The analysis methods used in this study require modest computing power and could be incorporated into microchips, personal digital assistants, or commercial monitors, making these tools readily available for clinical use. It is clear that there are several quite different ways to quantify what is generally called “heart-rate variability”, to include indices derived from spectral analysis (such as sympathovagal balance) and from complexity analysis (such as approximate entropy). Prospective, large-scale clinical trials will be needed to determine the clinical utility of these methods in guiding decision making, and to define the merits of these different approaches.

CONCLUSION

Loss of RRI complexity, as evidenced by decreased entropy, diminished fractal scaling, loss of short-term cor-

relations in the RRI, and higher similarity of distributions in the signal, characterized nonsurviving trauma patients and distinguished them from survivors. The fact that several computationally different methods pointed to loss of complexity in NonS lends additional weight to these findings. Prehospital loss of RRI complexity, measured by ApEn, was associated with mortality independent of the field GCS_{MOTOR} and hospital ISS. Evaluation of cardiovascular complexity may be useful for noninvasive, remote triage.

ACKNOWLEDGMENTS

We thank Denise Hinds, RN for patient data collection.

REFERENCES

- Holcomb JB, Niles SE, Miller CC, et al. Prehospital physiologic data and lifesaving interventions in trauma patients. *Mil Med.* 2005; 170:7–13.
- Akselrod S, Gordon D, Ubel FA, et al. Power spectrum analysis of heart rate fluctuation: a quantitative probe of beat-to-beat cardiovascular control. *Science.* 1981;213:220–222.
- Malliani A, Pagani M, Lombardi F, et al. Cardiovascular neural regulation explored in the frequency domain. *Circulation.* 1991; 84:482–492.
- Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation.* 1996;93:1043–1065.
- Butler GC, Yamamoto Y, Hughson RL. Fractal nature of short-term systolic BP and HR variability during lower body negative pressure. *Am J Physiol.* 1994;267:R26–R33.
- Goldstein B, Mickelsen D, Want A, et al. Effect of N(G)-nitro-L-arginine methyl ester on autonomic modulation of heart rate variability during hypovolemic shock. *Crit Care Med.* 1999; 27:2239–2245.
- Cooke WH, Convertino VA. Heart rate variability and spontaneous baroreflex sequences: implications for autonomic monitoring during hemorrhage. *J Trauma.* 2005;58:798–805.
- Goldstein B, Fiser DH, Kelly MM, et al. Decomplexification in critical illness and injury: relationship between heart rate variability, severity of illness, and outcome. *Crit Care Med.* 1998;26:352–357.
- Winchell RJ, Hoyt DB. Spectral analysis of heart rate variability in the ICU: a measure of autonomic function. *J Surg Res.* 1996; 63:11–16.
- Cooke WH, Salinas J, Convertino VA, et al. Heart rate variability and its association with mortality in prehospital trauma patients. *J Trauma.* 2006;60:363–370; discussion 370.
- Cooke WH, Salinas J, McManus JG, et al. Heart period variability in trauma patients may predict mortality and allow remote triage. *Aviat Space Environ Med.* 2006;77:1107–1112.
- Ravelli F, Antolini R. Complex dynamics underlying the human electrocardiogram. *Biol Cybern.* 1992;67:57–65.
- Goldberger AL, West BJ. Applications of nonlinear dynamics to clinical cardiology. *Ann N Y Acad Sci.* 1987;504:195–213.
- Lipsitz LA, Goldberger AL. Loss of ‘complexity’ and aging. Potential applications of fractals and chaos theory to senescence. *JAMA.* 1992;267:1806–1809.
- Batchinsky AI, Cooke WH, Kuusela T, et al. Loss of complexity characterizes the heart-rate response to experimental hemorrhagic shock in swine. *Crit Care Med.* 2007;35:519–525.
- Batchinsky AI, Cooke WH, Kuusela TA, et al. Sympathetic nerve activity and heart rate variability during severe hemorrhagic shock in sheep. *Auton Neurosci.* In press.
- West BJ, Scafetta N, Cooke WH, et al. Influence of progressive central hypovolemia on Holder exponent distributions of cardiac interbeat intervals. *Ann Biomed Eng.* 2004;32:1077–1087.
- Kuusela TA, Jartti TT, Tahvanainen KU, et al. Nonlinear methods of biosignal analysis in assessing terbutaline-induced heart rate and blood pressure changes. *Am J Physiol Heart Circ Physiol.* 2002; 282:H773–H783.
- Hayano J, Taylor JA, Mukai S, et al. Assessment of frequency shifts in R-R interval variability and respiration with complex demodulation. *J Appl Physiol.* 1994;77:2879–2888.
- Pincus S. Approximate entropy (ApEn) as a complexity measure. *Chaos.* 1995;5:110–117.
- Richman JS, Moorman JR. Physiological time-series analysis using approximate entropy and sample entropy. *Am J Physiol Heart Circ Physiol.* 2000;278:H2039–H2049.
- Peng CK, Havlin S, Stanley HE, et al. Quantification of scaling exponents and crossover phenomena in nonstationary heartbeat time series. *Chaos.* 1995;5:82–87.
- Zochowski M, Winkowska-Nowak K, Nowak A, et al. Autocorrelations of R-R distributions as a measure of heart variability. *Phys Rev E.* 1997;56:3725–3727.
- Pincus SM, Cummins TR, Haddad GG. Heart rate control in normal and aborted-SIDS infants. *Am J Physiol.* 1993;264:R638–R646.
- Hao B. Symbolic dynamics and characterization of complexity. *Physica D.* 1991;51:161–176.
- Glass L, Guevara MR, Perez R. Bifurcation and chaos in a periodically stimulated cardiac oscillator. *Physica D.* 1983;7:39–101.
- Goldberger AL, West BJ. Fractals in physiology and medicine. *Yale J Biol Med.* 1987;60:421–435.
- Elbert T, Ray WJ, Kowalik ZJ, et al. Chaos and physiology: deterministic chaos in excitable cell assemblies. *Physiol Rev.* 1994; 74:1–47.
- Goldberger AL, Giles F. Filley lecture. Complex systems. *Proc Am Thorac Soc.* 2006;3:467–471.
- Pincus SM. Greater signal regularity may indicate increased system isolation. *Math Biosci.* 1994;122:161–181.
- West BJ. Physiology in fractal dimensions: error tolerance. *Ann Biomed Eng.* 1990;18:135–149.
- Palazzolo JA, Estafanous FG, Murray PA. Entropy measures of heart rate variation in conscious dogs. *Am J Physiol.* 1998;274:H1099–H1105.
- Hogue CW Jr, Domitrovich PP, Stein PK, et al. RR interval dynamics before atrial fibrillation in patients after coronary artery bypass graft surgery. *Circulation.* 1998;98:429–434.
- Makikallio TH, Ristimae T, Airaksinen KE, et al. Heart rate dynamics in patients with stable angina pectoris and utility of fractal and complexity measures. *Am J Cardiol.* 1998;81:27–31.
- Mandelbrot BB. *Fractals, Form and Chance.* San Francisco: WH Freeman; 1977.
- Huikuri HV, Makikallio TH, Peng CK, et al. Fractal correlation properties of R-R interval dynamics and mortality in patients with depressed left ventricular function after an acute myocardial infarction. *Circulation.* 2000;101:47–53.
- Tapanainen JM, Thomsen PE, Kober L, et al. Fractal analysis of heart rate variability and mortality after an acute myocardial infarction. *Am J Cardiol.* 2002;90:347–352.
- Vikman S, Makikallio TH, Yli-Mayry S, et al. Altered complexity and correlation properties of R-R interval dynamics before the spontaneous onset of paroxysmal atrial fibrillation. *Circulation.* 1999;100:2079–2084.