

New Measures of Heart-Rate Complexity: Effect of Chest Trauma and Hemorrhage

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Background: Traditional vital signs such as heart rate, blood pressure, and oxygen saturation are not ideal for timely and accurate assessment of physiologic status after trauma (TR) and hemorrhagic shock (HS). Analysis of the complex beat-to-beat variability present in the heart-rate time series has been proposed as a “new vital sign” in this setting. We determined the effect of chest TR and HS on heart-rate complexity (HRC) in a porcine model.

Methods: Anesthetized swine in group II ($n = 20$) underwent blunt right chest TR with a modified captive-bolt stunner; then, 10 minutes later, hemorrhage of 12 mL/kg over 10 minutes, followed by resuscitation with lactated Ringer’s solution, and reinfusion of blood. Group I ($n = 15$) served as time controls. Two hundred beat sections of EKG waveforms were analyzed at 7 time points: at baseline, after TR, immediately after hemorrhage (HS), and 1 hour, 2 hours, 4 hours, and 5 hours after HS. Several computationally different measures of HRC were calculated, including sample entropy, similarity of distribution, and point correlation dimension.

Results: HRC was decreased after TR, HS, and at 1 hour, manifested by decreased sample entropy and point correlation dimension and increased similarity of distribution. These HRC measures were all restored by resuscitation.

Conclusions: Several independent measures demonstrated decreased HRC after combined TR/HS and restored HRC with resuscitation. Complexity analysis may be useful for diagnosis of TR/HS and for monitoring resuscitation.

Key Words: Pulmonary contusion, Hemorrhagic shock, Electrocardiography, Entropy, Complexity, Heart rate variability, Fractals, Nonlinear dynamics, Spectrum analysis.

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Timely and accurate diagnosis of severity of injury in patients with trauma is an unresolved problem both in civilian and military settings.^{1,2} Currently used diagnostic and

monitoring tools in the prehospital environment include physical examination and vital signs, such as the heart rate, blood pressure, and oxygen saturation. These tools are often inadequate, however, to reliably assess injury severity³ or the need to perform life-saving interventions,⁴ which may lead to triage errors in patients with prehospital trauma.⁵ On the battlefield, furthermore, direct contact with a casualty may need to be postponed during combat. To meet this challenge, the concept of “remote triage” has been proposed. This involves the categorization of patients by analysis of telemeasured data such as the R-to-R interval (RRI) derived from the EKG or the systolic arterial pressure (SAP) time series derived from the blood pressure wave form. In particular, beat-to-beat changes in the RRI are an untapped source of additional information about casualty status.

One approach to extracting as much information as possible from the RRI signal involves use of measures from nonlinear dynamics.^{6–8} These methods allow assessment of the complex variability present in the RRI signal. We previously examined several such methods suitable for assessment of heart-rate complexity (HRC) and found that they changed with volume status during hemorrhagic shock (HS) in swine⁹ and in sheep.¹⁰ Changes in SAP variability during hypovolemia were less pronounced and confined to decrease in SAP high frequency power.⁹ We also demonstrated that loss of HRC, as assessed by variables which measure signal irregularity—approximate entropy (ApEn)¹¹ and sample entropy (SampEn)¹²—is associated with mortality in patients with prehospital trauma³ and with hypovolemia in burn patients.¹³ In several studies, we found HRC, as measured by SampEn, to be more diagnostically accurate than the traditional vital signs.^{3,4,13}

One of the new HRC measures is point correlation dimension (PD2i), that quantifies changes in the degrees of freedom of cardiovascular regulation.¹⁴ Degrees of freedom are calculated from RRI phase space plots and represent cardiovascular controllers. Hence, decrease in the degrees of freedom is a reflection of decreased HRC. This new wave form analysis technique has been applied in animal^{14,15} and human studies,^{16,17} and was found to separate patients at risk for lethal arrhythmias.^{16,18} The algorithm is currently FDA approved as a tool to measure autonomic status in humans.

Our previous work suggested that HRC could be used as a sensitive “new vital sign” for assessment of critically injured patients, thus facilitating more accurate and earlier diagnosis and treatment decisions.³ However, patients with trauma frequently incur a combination of injury (TR) and

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James Skinner and Daniel Weiss are employees of Vicor Technologies that developed the Point Correlation Dimension method used in this study.

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hemorrhage shock (HS). There have been no controlled studies of the combined effects of TR/HS on changes in HRC in any species. The objective of this study was to determine whether loss of complexity, as assessed by SampEn, PD2i, and other complementary measures, occurs in a porcine model of TR and HS. We hypothesized that HRC is decreased after TR and subsequent HS and is restored with resuscitation. In addition, we also evaluated SAP variability using the same complexity measures.

MATERIALS AND METHODS

This study was approved by the US Army Institute of Surgical Research Animal Care and Use Committee and was performed in accordance with the guidelines set forth by the Animal Welfare Act, other federal statutes and regulations, and by the 1996 *Guide for the Care and Use of Laboratory Animals* of the National Research Council.

Animal Preparation

Female Yorkshire pigs ($n = 35$) weighing 31.1 ± 0.8 kg SEM were fasted, premedicated with ketamine (1 mg/kg), and intubated. Under isoflurane anesthesia, a tracheostomy was performed; the right carotid artery, right external jugular vein, and both femoral arteries and veins were cannulated; and a Foley catheter was placed. At completion of surgery, total intravenous anesthesia was initiated (ketamine, 200 mcg/kg/min and propofol, 100 mcg/kg/min) and continued throughout the experiment. Anesthesia was maintained at a constant level in both groups to minimize its effects on calculated variables. The animals were placed on a Siemens Servo 300 A ventilator (Siemens-Elema AB, Sweden) in the volume-control mode, at a tidal volume of 12 mL/kg, respiratory rate of 12 per min, FiO_2 of 50%, and positive end expiratory pressure of 0. Respiratory rate was adjusted to provide normocapnia ($\text{Paco}_2 = 35\text{--}45$ mm Hg).

Experimental Protocol

After 1 to 2 hours of stabilization in the ICU, in the injured group (Group II, $n = 20$) right-sided chest trauma was induced at end inspiration, using a modified captive-bolt humane stunner (Model MKL, Karl Schermer, Packers Engineering, Omaha, NE) as previously described by Proctor and coworkers.^{19,20} A chest tube was immediately placed on the side of the impact. Ten minutes after pulmonary contusion, the animals underwent a constant-rate 12 mL/kg hemorrhage (corresponding $\sim 20\%$ of total blood volume) over 10 minutes. The withdrawn blood was stored in citrated infusion bags. After a 30-minute shock period, resuscitation with three times the shed blood volume of lactated Ringers' solution was performed. Then, the shed blood was reinfused. Total resuscitation time was 30 minutes to 40 minutes. A maintenance infusion of lactated Ringers' (4 mL/h for first 10 kg, 2 mL/h for next 10 kg, and 1 mL/h for additional kg) was then started, and adjusted to maintain a urine output of 0.5 mL/kg/h. Animals dying on impact or later during the experiment were excluded from the study. Animals in the control group (Group I, $n = 15$) were treated identically with respect to premedication, anesthesia, instrumentation, general timeline, and maintenance fluid administration, but received no TR,

HS, resuscitation, or tube thoracostomy. After completion of the protocol animals were euthanized by an overdose of sodium pentobarbital (Fatal-Plus, Vortech Pharmaceuticals Inc., Dearborn, MI).

Data Analysis

The EKG of all animals was continuously monitored and recorded at 500 Hz to a personal computer using a DREW data acquisition system (US Army Institute of Surgical Research, San Antonio, TX). EKG and blood-pressure wave form analysis was conducted at seven discrete time points: during baseline, after TR, immediately after completion of hemorrhage (HS), and 1 hour, 2 hours, 4 hours, and 5 hours after completion of hemorrhage. The HS time point represented data acquired immediately after completion of blood withdrawal, whereas the 1- and 2-hour time points were taken immediately after resuscitation and blood reinfusion, respectively. For each time point, 200-beat sections of EKG and blood-pressure waveforms were imported into WinCPRs software (Absolute Aliens Oy, Turku, Finland) and analyzed as previously described.⁹ These data sets were the longest ectopy-free data segments that could be identified consistently in all animals in this experiment. Methodological and clinical validity of use of 200-beat data sets was previously verified for HRC analysis.^{12,21–23} Description of the analyses used has been previously reported.^{3,9} Briefly, automatic identification of R waves was performed by an isoelectric line-shift algorithm. Manual verification of R-wave detection and screening for ectopic beats was performed. Only data sets free of ectopic beats were analyzed. Next, the software generated the instantaneous RRI and SAP time series. Blood-pressure variability was analyzed in a manner analogous to the heart rate; for the heart rate, the variability in the RRI was analyzed, whereas for the blood pressure, the beat-to-beat variability in the SAP was analyzed.

Nonlinear Analysis Techniques

HRC variables were calculated for the same 200-beat segments using the software as previously reported (Table 1).^{3,9} In addition, we calculated the PD2i, which measures the time-dependent nonstationary changes in the degrees of freedom of a data series.^{14,15} The degrees of freedom are a measure of the number of independent variables that are currently producing the data series, and they can be fractional, as in the chaotic data produced by the Lorenz generator ($\text{df} = 2.06$), or integers, as in the data produced by a sine-wave generator ($\text{df} = 1.0$).

In this study, PD2i analysis was performed using proprietary automated software (Vicar 2.0, Vicor Technologies, Inc., Boca Raton, FL) that takes the EKG as input, determines the RRIs, uses several noise analyses, and then calculates the PD2i.^{14,15,24} A common rule ($\text{Ni} > 10 \exp \text{PD2i}$) was used for determining the minimum number of data points to resolve a given number of degrees of freedom.²⁵ In this case where $\text{Ni} = 200$ RRI, the rule indicates that the degrees of freedom between 0 and 2 can be accurately resolved. The same PD2i parameters were used in the version of the software used for calculation in this study (Vicar 2.0) as in previous publica-

TABLE 1. Variable Definitions

Calculated Variables (Abbreviations)	Variable Name	Comment
SampEn, ApEn	Sample entropy and approximate entropy	Measure the likelihood of finding similar patterns in the signal. Lower entropy implies a more regular and less complex signal.
PD2i	Point correlation dimension	Measures time-dependent changes in the degrees of freedom of a data series. A lower PD2i number signifies loss of regulatory complexity.
SOD	Similarity of distributions	Calculates the probability of similar RRI signal amplitude distributions as a function of time. Higher SOD means more similar distribution and thus less complex regulation.
FDDA, FDCL	Fractal dimension by dispersion analysis and by curve lengths	Measures of self-similarity in the signal structure at various scales. Lower number implies lower complexity of signal regulation.
DisnEn	Symbol distribution entropy	The signal is represented in phase space as a sequence of symbols. The lower the entropy of this distribution the more predictable the signal and less complex its regulation.
FW	Percentage of forbidden words	The above sequence of symbols is put into “words.” Words that are not likely to occur in a signal are called forbidden. The higher the number of forbidden words the lower the system complexity.
StatAv	Stationarity	Measures changes in the mean and SD of the signal in a data set. The more stationary the StatAv signal the lower the number and vice versa.
TP	Total power	Total power of periodic oscillations in the ECG as determined by Fast Fourier Transform. Represents total heart rate variability along all frequency ranges.
LF	Low frequency power	A measure of the power of periodic oscillations in the ECG in the low frequency range reflecting both sympathetic and parasympathetic influences on the heart.
HF	High frequency power	A measure of the power of periodic oscillations in the ECG in the high frequency range reflecting vagal influence on the heart.
CDM LF	Low frequency amplitude by complex demodulation	A measure of the amplitude of periodic oscillations in the ECG in the low frequency range reflecting both sympathetic and vagal influences on the heart.
CDM HF	High frequency amplitude by complex demodulation	A measure of the amplitude of periodic oscillations in the ECG in the high frequency range reflecting vagal influences on the heart.

TABLE 2. Nonlinear Analysis Results for the RRI Signal

Variable	Group	Baseline	TR	HS	1 h	2 h	4 h	5 h
HR	I	85 ± 10	85 ± 10	84 ± 10	80 ± 9	78 ± 9	76 ± 9	77 ± 9
	II	98 ± 7	132 ± 8*	156 ± 9*	113 ± 6†	107 ± 6	95 ± 4	97 ± 4
SampEn	I	1.24 ± 0.09	1.32 ± 0.08	1.34 ± 0.07	1.28 ± 0.07	1.40 ± 0.08	1.20 ± 0.08	1.32 ± 0.10
	II	1.27 ± 0.05	1.02 ± 0.07‡	0.93 ± 0.04*	1.06 ± 0.06†	1.34 ± 0.06	1.35 ± 0.07	1.22 ± 0.08
PD2i	I	0.97 ± 0.13	1.29 ± 0.20	1.10 ± 0.19	1.19 ± 0.18	1.12 ± 0.20	1.09 ± 0.23	1.08 ± 0.25
	II	1.22 ± 0.13	0.60 ± 0.03†	0.53 ± 0.03*	0.62 ± 0.06*	0.68 ± 0.09	0.73 ± 0.08	0.70 ± 0.07
DisnEn	I	0.72 ± 0.01	0.76 ± 0.01	0.74 ± 0.02	0.72 ± 0.02	0.76 ± 0.02	0.70 ± 0.03	0.73 ± 0.03
	II	0.73 ± 0.02	0.60 ± 0.03*	0.67 ± 0.02†	0.70 ± 0.02	0.73 ± 0.02	0.75 ± 0.02	0.68 ± 0.02
SOD	I	0.17 ± 0.02	0.14 ± 0.01	0.15 ± 0.02	0.12 ± 0.01	0.17 ± 0.01	0.19 ± 0.01	0.19 ± 0.02
	II	0.16 ± 0.01	0.21 ± 0.02‡	0.29 ± 0.02*	0.27 ± 0.02*	0.20 ± 0.01	0.21 ± 0.01	0.21 ± 0.02
FDDA	I	1.29 ± 0.06	1.25 ± 0.05	1.28 ± 0.05	1.21 ± 0.05	1.26 ± 0.04	1.18 ± 0.02	1.19 ± 0.05
	II	1.22 ± 0.03	1.10 ± 0.02†	1.20 ± 0.05	1.14 ± 0.03	1.15 ± 0.02†	1.13 ± 0.02	1.15 ± 0.03
FDCL	I	1.84 ± 0.03	1.85 ± 0.02	1.82 ± 0.02	1.81 ± 0.03	1.81 ± 0.02	1.81 ± 0.03	1.81 ± 0.03
	II	1.83 ± 0.02	1.62 ± 0.05*	1.76 ± 0.03	1.75 ± 0.02	1.78 ± 0.02	1.76 ± 0.03	1.72 ± 0.03
FW	I	54.67 ± 2.02	49.40 ± 2.41	49.87 ± 3.14	50.13 ± 2.05	47.13 ± 2.90	49.07 ± 3.24	50.40 ± 3.72
	II	50.10 ± 2.43	60.21 ± 2.85†	56.45 ± 2.59	51.65 ± 2.91	49.20 ± 2.83	48.10 ± 2.61	55.60 ± 2.89
StatAv	I	0.55 ± 0.08	0.58 ± 0.06	0.59 ± 0.06	0.64 ± 0.05	0.59 ± 0.06	0.65 ± 0.05	0.70 ± 0.07
	II	0.62 ± 0.04	0.83 ± 0.05†	0.67 ± 0.06	0.75 ± 0.04	0.70 ± 0.05	0.76 ± 0.03	0.74 ± 0.05

Group I, controls; Group II, injured. Timepoints: TR, after chest trauma; HS, after 12 mL/kg bleed; 1 h, 2 h, 4 h, 5 h, times in hours after end of HS; HR, heart rate (beats/min); SampEn, sample entropy; PD2i, point correlation dimension; DisnEn, normalized symbol-distribution entropy; SOD, similarity of distributions; FDDA, fractal dimension by dispersion analysis; FDCL, fractal dimension by curve lengths; FW, percentage of forbidden words (%); StatAv, stationarity measures in arbitrary units. Data are means ± SEM. Significance by two-tailed *t* test.

Significance levels: * *p* < 0.001, † *p* < 0.05; ‡ *p* < 0.01.

tions (Tau = 1, linearity criterion [LC] = 0.30, convergence criterion [CC] = 0.40, plot length [PL] = 0.15, and plot interval [PI] = 4).^{14,15,24} Outliers >2.8 SDs from the mean were removed from the RRI series by a linear interpolation spline.

Linear Analysis Techniques

Although the focus in this study was on nonlinear techniques, we also performed frequency-domain analysis by fast Fourier transform,^{9,26} calculating total power (TP) over 0.003 Hz·ms² to 0.4 Hz·ms²; low frequency (LF) power over 0.05 Hz·ms² to 0.15 Hz·ms²; and high-frequency (HF) power over 0.15 Hz·ms² to 0.4 Hz·ms². We also measured the amplitudes of the low frequency (CDM LF) and high frequency (CDM HF) oscillations by the method of complex demodulation.^{3,13,27}

Statistical Analysis

Statistical analysis was performed using the software package SAS version 9.1 (SAS Institute, Cary, NC). Groups were compared at each time point using a Student's *t* test or the nonparametric Wilcoxon test where appropriate. The null hypothesis was rejected at the 5% probability level.

RESULTS

TR and subsequent HS caused tachycardia at the TR, HS, and 1-hour time points (Table 2). Hypotension was observed after TR and HS, and the SAP remained somewhat lower in injured than in control animals until the end of the study (Table 3). Blood loss through the chest tube was negligible.

Changes in HRC are provided in Table 2. TR and then HS caused loss of HRC by several measures, which was

reversed by resuscitation. Thus, SampEn (Fig. 1) and PD2i (Fig. 2) were lower at the TR, HS, and 1-hour time points but were not different between groups thereafter. Normalized symbol-distribution entropy (DisnEn) was lower after TR and HS. Similarity of distribution (SOD) was higher after TR, HS, and at 1 hour, decreasing thereafter to levels not different from those in group I (Fig. 3). Fractal dimension by curve lengths (FDCL) was lower after TR and fractal dimension by dispersion analysis (FDDA) was lower after TR and 2-hour time points in group II (Table 2). FW and stationarity measures in arbitrary units were higher after TR in group II.

Changes in SAP complexity are provided in Table 2 and included lower SampEn after HS; lower DisnEn after TR; and lower FDCL after both TR and HS. FDDA did not

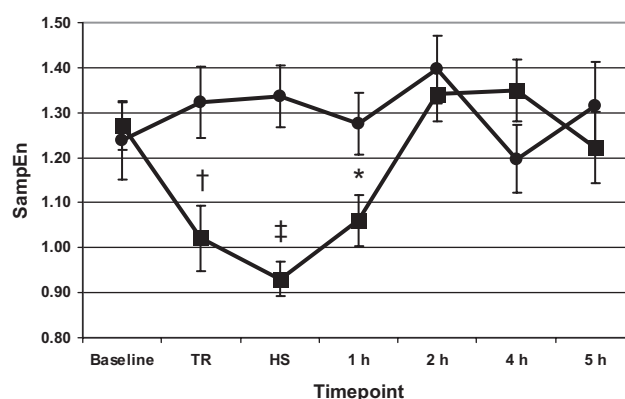


Figure 1. Changes in RRI SampEn in injured (squares) vs. controls (circles). Significance by two-tailed *t* test: **p* < 0.05; †*p* < 0.01; ‡*p* < 0.001.

TABLE 3. Nonlinear Analysis Results for the SAP Signal

Variable	Group	Baseline	TR	HS	1 h	2 h	4 h	5 h
CVP	I	3.2 ± 0.5	3.0 ± 0.5	2.7 ± 0.4	2.7 ± 0.5	2.9 ± 0.6	2.7 ± 0.6	3.1 ± 0.7
	II	2.6 ± 0.5	1.96 ± 0.4	1.32 ± 0.4*	4.7 ± 0.6*	4.7 ± 0.7	6.05 ± 0.8†	5.1 ± 0.7*
SAP	I	120 ± 3	121 ± 3	120 ± 3	122 ± 3	122 ± 3	120 ± 3	118 ± 3
	II	120 ± 3	79 ± 4‡	69 ± 3‡	112 ± 3*	105 ± 3‡	106 ± 2‡	105 ± 3†
SampEn	I	0.54 ± 0.08	0.54 ± 0.09	0.55 ± 0.09	0.57 ± 0.07	0.54 ± 0.08	0.54 ± 0.06	0.61 ± 0.08
	II	0.53 ± 0.07	0.55 ± 0.07	0.32 ± 0.02*	0.50 ± 0.05	0.52 ± 0.06	0.55 ± 0.4	0.71 ± 0.07
DisnEn	I	0.67 ± 0.01	0.70 ± 0.01	0.69 ± 0.01	0.69 ± 0.02	0.71 ± 0.01	0.71 ± 0.01	0.71 ± 0.02
	II	0.71 ± 0.01	0.66 ± 0.02*	0.66 ± 0.00	0.70 ± 0.01	0.70 ± 0.01	0.71 ± 0.01	0.72 ± 0.01
SOD	I	0.12 ± 0.01	0.11 ± 0.00	0.11 ± 0.00	0.11 ± 0.00	0.11 ± 0.00	0.11 ± 0.00	0.12 ± 0.00
	II	0.12 ± 0.00	0.11 ± 0.00	0.12 ± 0.00	0.11 ± 0.00	0.12 ± 0.01	0.11 ± 0.00	0.11 ± 0.01
FDDA	I	1.54 ± 0.06	1.60 ± 0.05	1.61 ± 0.05	1.52 ± 0.04	1.58 ± 0.05	1.60 ± 0.06	1.58 ± 0.06
	II	1.54 ± 0.04	1.47 ± 0.07	1.69 ± 0.04	1.58 ± 0.05	1.53 ± 0.05	1.51 ± 0.04	1.46 ± 0.05
FDCL	I	1.95 ± 0.02	1.95 ± 0.01	1.95 ± 0.01	1.92 ± 0.01	1.94 ± 0.01	1.94 ± 0.01	1.94 ± 0.01
	II	1.94 ± 0.01	1.89 ± 0.01*	1.92 ± 0.01*	1.92 ± 0.01	1.92 ± 0.01	1.93 ± 0.01	1.92 ± 0.01
FW	I	63.33 ± 2.19	60.87 ± 2.31	61.27 ± 2.68	62.13 ± 2.07	61.27 ± 2.21	59.93 ± 1.95	58.33 ± 2.87
	II	60.00 ± 2.15	65.05 ± 1.41	69.85 ± 0.74†	61.20 ± 1.52	62.15 ± 1.71	60.05 ± 1.55	57.05 ± 1.96
StatAv	I	0.27 ± 0.06	0.23 ± 0.03	0.21 ± 0.03	0.27 ± 0.04	0.23 ± 0.04	0.25 ± 0.05	0.26 ± 0.04
	II	0.25 ± 0.03	0.38 ± 0.06*	0.17 ± 0.02	0.24 ± 0.24	0.30 ± 0.05	0.28 ± 0.04	0.33 ± 0.05

Group I, controls; Group II, injured. Timepoints: TR, after chest trauma; HS, after 12 mL/kg bleed; 1 h, 2 h, 4 h, 5 h, times in hours after end of HS; CVP, central venous pressure (mm Hg); SampEn, sample entropy; DisnEn, normalized symbol-distribution entropy; SOD, similarity of distributions; FDDA, fractal dimension by dispersion analysis; FDCL, fractal dimension by curve lengths; FW, percentage of forbidden words (%); StatAv, stationarity. Measures in arbitrary units. Data are means ± SEM. Significance by two-tailed *t* test. Significance levels: **p* < 0.05; †*p* < 0.01; ‡*p* < 0.001.

change. FW and stationarity measures in arbitrary units were higher after HS and TR, respectively (Table 3).

Frequency domain and complex demodulation results for RRI are shown in Table 4. TR and HS caused a

decrease in TP, LF, and CDM LF, all of which persisted through 1 hour (Table 4). HF (Fig. 4) and CDM HF were also lower after TR and HS. This persisted through the 4-hour time point (Table 4).

Frequency domain and complex demodulation results for SAP are shown in Table 5. TP, HF, and CDM HF were higher after TR and HS and were restored to values not different from controls by resuscitation.

DISCUSSION

In this study, we performed comprehensive physiologic wave form analysis using nonlinear dynamics tools (and traditional frequency-domain methods) in a clinically relevant porcine model of combined chest trauma and HS (TR/HS). The principal finding is that HRC, to include an irregularity metric (SampEn) and a measure of the dimensions of regulation (PD2i), decreased after TR/HS and was restored by resuscitation. Changes in HRC were independent of changes in HF, which remained depressed despite resuscitation. SAP complexity also decreased in this model, but the changes were less pronounced.

Assessment of cardiovascular regulatory complexity by means of nonlinear analysis of the structural complexity of

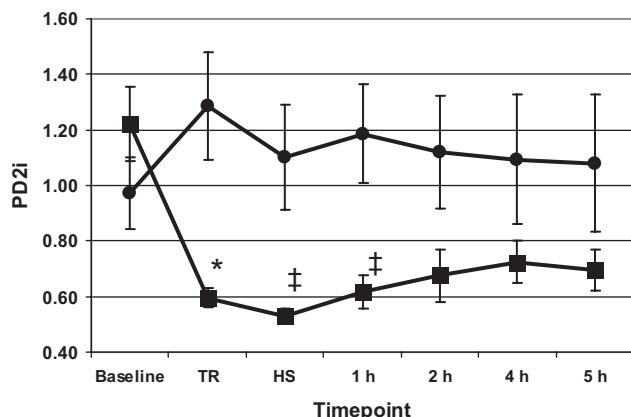


Figure 2. Changes in RRI PD2i in injured vs. controls. Significance by two-tailed *t* test: **p* < 0.05; †*p* < 0.01; ‡*p* < 0.001.

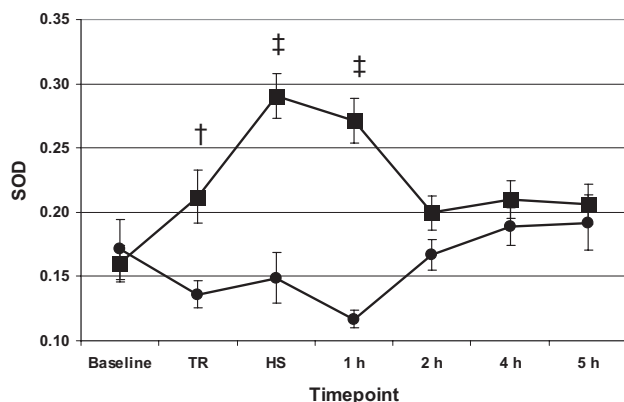


Figure 3. Changes in RRI SOD in injured (squares) vs. controls (circles). Significance by two-tailed *t* test: †*p* < 0.01; ‡*p* < 0.001.

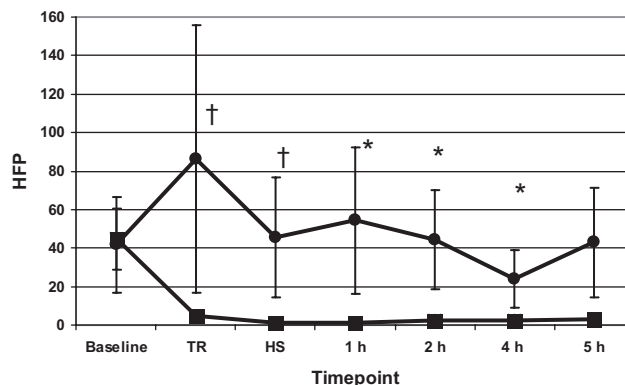


Figure 4. Changes in RRI HF in injured (squares) vs. controls (circles). Significance by two-tailed *t* test: **p* < 0.05; †*p* < 0.01.

TABLE 4. Frequency-Domain Analysis Results for the RRI Signal

Variable	Group	Baseline	TR	HS	1 h	2 h	4 h	5 h
RRI TP	I	106 ± 56	140 ± 97	81 ± 43	87 ± 44	72 ± 35	56 ± 24	81 ± 38
	II	94 ± 30	38 ± 23*	7 ± 3†	7 ± 2*	17 ± 6	13 ± 3	17 ± 5
LF	I	53 ± 31	23 ± 15	16 ± 7	8 ± 3	9 ± 4	10 ± 5	11 ± 5
	II	9 ± 2	10 ± 9*	1.5 ± 0.9†	0.7 ± 0.2‡	2 ± 1	2 ± 0.3	1.8 ± 0.5
HF	I	42 ± 25	86 ± 70	46 ± 31	54 ± 38	44 ± 26	24 ± 15	43 ± 28
	II	45 ± 16	4.6 ± 2.8*	1 ± 0.2*	1 ± 0.2‡	2.5 ± 0.7‡	2.3 ± 0.5‡	3.3 ± 1.2
CDM LF	I	3.9 ± 1.2	3.9 ± 1.0	4.9 ± 1.5	2.7 ± 0.6	2.9 ± 0.7	2.5 ± 0.5	2.7 ± 0.8
	II	2.9 ± 0.5	2.4 ± 1.1‡	1.2 ± 0.3*	1.1 ± 0.1*	1.5 ± 0.3	1.6 ± 0.2	1.5 ± 0.2
CDM HF	I	4.4 ± 1.2	7.3 ± 2.8	5.8 ± 1.9	6.1 ± 1.8	6.3 ± 1.9	4.7 ± 1.3	5.5 ± 2
	II	7.0 ± 1.4	2.1 ± 0.4‡	1.4 ± 0.2*	1.7 ± 0.1‡	2.1 ± 0.2‡	1.9 ± 0.2‡	2 ± 0.3

Group I, controls; Group II, injured. Time points: TR, after chest trauma; HS, after 12 mL/kg bleed; 1 h, 2 h, 4 h, 5 h, times in hours after end of HS; RRI, R-to-R interval of the EKG; RRI TP, total R-to-R interval spectral power (0.003–0.4 Hz ms²); LF, spectral power at the low frequency (0.05–0.15 Hz ms²); HF, spectral power at the high frequency (0.15–0.4 Hz ms²); CDM LF, amplitude of the LF oscillations by complex demodulation; CDM HF, amplitude of the HF oscillations by complex demodulation. Data are means ± SEM. Significance by two-tailed *t* test.

Significance levels: **p* < 0.01; †*p* < 0.001; ‡*p* < 0.05.

TABLE 5. Frequency-Domain Results for the SAP Signal

Variable	Group	Baseline	TR	HS	1 h	2 h	4 h	5 h
SAP TP	I	9 ± 2	9.5 ± 2	11 ± 3	13 ± 4	11 ± 2	12 ± 1	13 ± 3
	II	15 ± 3	28 ± 5*	50 ± 7*	15 ± 6	12 ± 3	8 ± 2†	7 ± 1†
LF	I	3 ± 1	3 ± 1	3 ± 2	1 ± 1	1 ± 0.8	1 ± 1	1 ± 1
	II	1 ± 0.8	3 ± 2.5	2 ± 1.9	0.1 ± 0	0.1 ± 0.1	0.1 ± 0.0†	0.1 ± 0.0†
HF	I	5.6 ± 1.8	6 ± 2	7.5 ± 3	11 ± 4	10 ± 2	10 ± 1	10 ± 2
	II	12.9 ± 3.5	20 ± 4‡	47 ± 7*	14 ± 5	11 ± 3	7 ± 1	6 ± 1
CDM LF	I	1.3 ± 0.5	1.3 ± 0.5	1 ± 0.5	0.8 ± 0.3	0.5 ± 0.3	0.6 ± 0.3	0.9 ± 0.4
	II	0.5 ± 0.1	1 ± 0.3	0.6 ± 0.2	0.3 ± 0.1†	0.4 ± 0.1	0.4 ± 0.1	0.3 ± 0.1
CDM HF	I	3 ± 0.4	3 ± 0.4	3.3 ± 0.5	3.8 ± 0.5	4.2 ± 0.5	4.3 ± 0.3	4.4 ± 0.4
	II	4.5 ± 0.5†	6 ± 0.6‡	9.2 ± 0.7*	4.5 ± 0.6	3.9 ± 0.5	3.5 ± 0.3	3.3 ± 0.3

Group I, controls; Group II, injured. Timepoints: TR, after chest trauma; HS, after 12 mL/kg bleed; 1 h, 2 h, 4 h, 5 h, times in hours after end of HS; SAP TP, total SAP spectral power (0.003–0.4 Hz ms²); LF spectral power at the low frequency (0.05–0.15 Hz ms²); HF spectral power at the high frequency (0.15–0.4 Hz ms²); CDM LF, amplitude of the LF oscillations by complex demodulation; CDM HF, amplitude of the HF oscillations by complex demodulation. Data are means ± SEM. Significance by two-tailed *t* test.

Significance levels: * *p* < 0.001; † *p* < 0.05; ‡ *p* < 0.01.

the RRI and SAP signals is a relatively new concept in physiologic monitoring. Signal complexity may be assessed by methods that assess the structural patterns, scaling phenomena, dimensions, or amplitudes embedded within the signal.^{9,28} Such analyses offer a “window” into the changes occurring in underlying regulatory processes, which are thought to involve multiple neurohormonal feedback loops, which are hierarchically organized into cascading levels.^{17,29,30} We think that these distinct HRC measures contribute to a multifaceted view of overall cardiovascular health and adaptability to stress. Because nonlinearity is an intrinsic feature of sympathetic-parasympathetic interactions³¹ and of the cardiovascular system as a whole,^{8,29} wave form analysis techniques based on nonlinear statistical methods are specifically useful for quantification of the complex changes in state of the subject.^{8,9,28} In this study, the entropy measures of HRC that assess the degree of irregularity or randomness of the signal all decreased in the injured group, signifying presence of a more regular or less random signal with TR and HS. A less random signal structure is thought to reflect less regulatory feedback in response to TR and HS. These results are in line with our previous work in swine, in which HS alone was associated with decreased SampEn, which was reversed by resuscitation.⁹ Similarly, humans in burn shock had low HRC upon admission which then improved with fluid resuscitation.¹³ These studies and others^{10,32–34} demonstrate that restoration of volume status is characterized by increased irregularity of the RRI signal. Whether this variable could be used as an index of resuscitation adequacy remains to be determined.

Recent investigations of HRC during trauma included our work in patients with prehospital trauma. HRC as assessed by SampEn and ApEn were lower in more severely injured individuals who eventually died compared with lesser injured survivors.³ Using a different cohort of patients with trauma, Cancio et al.⁴ found lower values of SampEn in more severely injured patients with trauma that required performance of life-saving interventions as compared with less injured patients. A prospective clinical trial making use of this observation will be initiated soon and that trial will also

use calculation of entropy along multiple scales using longer data sets,³⁵ which we recently added to our tool kit.

In this study, for the first time we also investigated PD2i.^{14,17} The Correlation Dimension concept models the cardiovascular system as a stationary strange attractor, plots its position in phase space, and quantifies a decrease in the dimensions of regulation of this system as a decrease in the number of states of the system in phase space.¹⁴ Thus, a more complex signal is a reflection of a higher number of dimensions of regulation or feedback loops in action, whereas a lower correlation dimension points to a decreased complexity of regulation and fewer feedback loops involved.

PD2i enables continuous monitoring of changes in degrees of freedom (dimensions) of the cardiovascular attractor.^{14,17} PD2i is thought to measure the degree of interaction or “cooperation” among the various feedback loops that control the HR.^{14,17} Breakdown of the couplings among these autonomic neural loops is denoted by lower PD2i values. PD2i has been applied under various conditions including HS in rats, myocardial ischemia in pigs, and human cardiac patients.^{14–16} During these conditions, the degrees of freedom of cardiovascular regulation decrease as evidenced by lower PD2i values.^{14,16} In this study, PD2i showed the most profound decrease after TR; continued to decrease reaching a nadir after HS; and remained decreased at 1 hour. These changes in PD2i complement the overall finding of reduced HRC and are in line with previous work by Skinner et al.¹⁴ who identified decrease in PD2i in a rat model of HS.

The decrease in RRI DisnEn and the increase in RRI FW calculated from symbol dynamics strengthen our observations of reduced HRC after TR/HS, because these methods are methodologically distinct from the other complexity metrics.^{33,36} Further evidence supportive of loss of HRC in this study is the decrease in RRI FDCL and FDDA in the injured group, both of which quantify the fractal self-similarity of the signal.²⁸ However, fractal scaling methods seem to perform inconsistently²⁸ and should be applied with caution.

Our observation of reduced HRC after TR and HS was also solidified by the increase in the similarity of RRI signal

distributions (SOD; Fig. 3). These findings are encouraging with respect to SOD as an HRC metric, especially considering that it performs well with short, interrupted, and nonstationary data sets.^{3,21–23}

Consistent with our previous work in animals during HS,^{9,10} our current experiment shows a persistent decrease not only in the power of vagal input to the heart (RRI HF, Fig. 4) but also in its amplitude as assessed by CDM HF—a complementary measure of vagal input to the heart. Previous work^{3,4,9,13,33,37} suggests that decreased vagal modulation of the heart may be an important cause of decreases in both RRI HF and in RRI entropy (SampEn and ApEn). However, in this study HRC returned to levels not different from controls with resuscitation, whereas HF and CDM HF did not. This suggests that HRC is not merely a function of vagal input to the heart, but that it carries additional information about cardiovascular status.

Changes in SAP HF and SAP CDM HF likely can be explained by the well-known effect of positive-pressure mechanical ventilation on blood-pressure variability in hypovolemic subjects.^{38,39} Briefly, blood pressure oscillations, induced by positive-pressure inhalation, are more prominent in hypovolemia. Both the hypotension and the changes in HRC observed in this study began after TR and before the onset of HS. Hypotension began immediately upon impact and reached a nadir at 30 seconds to 60 seconds thereafter (data not shown). Blood loss via the chest tube was negligible, and overt signs of bleeding were not present. Intrapleural hematomas were not present at necropsy. The mechanisms responsible for such posttraumatic hypotension may include release of vasoactive mediators upon pulmonary contusion or decreased stroke volume in the setting of increased right heart afterload or both. Regardless of the pathophysiology, this study indicates that HRC may decrease not only in the setting of hypovolemia but also during other processes which impair cardiovascular function. In our previous studies in human patients with trauma injury, severity was marked by more pronounced decreases in HRC despite no differences in blood pressure. This underlines the nonspecific nature of HRC as a collective cardiovascular measure of health and of the ability to withstand critical perturbations.

Taken together, our previous and current work points to the potential use of HRC for assessment of injury severity, monitoring of resuscitation, and recovery in patients with trauma. HRC should be looked upon as a cumulative vital sign that is assessed by different nonlinear methods. It is important to note that use of different complementary methods provides particular strength to the overall approach. Although some of the methods used are redundant in their informational content (ApEn and SampEn) several others are methodologically distinct (SOD and PD2i). Because each method has its particular requirements in terms of minimal data set usable for a valid measure, concurrent use of these methodologically distinct tools increases the reliability of HRC assessment.

The 200-beat data sets used in this study are the longest data sets that were available for analysis in this experiment and are shorter than those used in some previous reports that used 800 heartbeats for the calculation of nonlinear met-

rics.^{3,9,10,13} However, we recently established that 200 beats are sufficient for accurate prediction of mortality in patients with trauma.^{22,23} Thus, we anticipate that 200-beat data sets are sufficient for the determination of changes in HRC and cardiovascular regulatory adjustments during many trauma applications. The data sets used in this study are also shorter than the 5 minutes of data recommended for frequency-domain analysis, which means that those results should be interpreted with caution.²⁶ Use of anesthesia may affect the variables calculated from physiologic waveforms.^{14,40} We used careful anesthesia titration via hourly performance of pinch tests, control of jaw tone, and cardiovascular monitoring and believe that level of anesthesia affected both experimental groups equally. Thus, our findings are unlikely to be caused by use of anesthetics and are more likely to be a true reflection of the profound physiologic perturbations caused by trauma, HS, and resuscitation. Breathing frequency and depth also have profound effects on heart-rate variability and complexity analysis and are recommended to be controlled in experimental setting.^{9,41} Because we used mechanical ventilation in our experiment and did not change the settings after injury we think that our findings were not a reflection of mechanical ventilation.⁴² Changes in HRC might be different in civilian trauma victims and combat casualties who are not mechanically ventilated. We are currently investigating the specific effects of paced as opposed to spontaneous breathing in a model of severe HS.

This study did not use continuous sliding window data analysis. Instead, we chose to analyze discrete data sets sampled during maximally stationary time points that followed dynamically changing conditions, such as trauma, hemorrhage, and resuscitation. A major and underappreciated caveat in continuous analysis of biosignals is real-time assessment of signal quality and nonstationarity—both of which, if not accounted for, can jeopardize the validity of results. Along these lines we think that discrete data analysis of “snapshots” of information as featured in this and previous studies by our group performed on ectopy-free data sets will retain its value as we search for reliable continuous analysis tools that are able to deal with spurious R-wave detection, presence of ectopy, and signal nonstationarity. An additional benefit of the discrete analysis approach is that it permits direct comparison of results acquired in different animal and human studies where data analysis followed the same consistent approach.^{3,4,9,10,13,22,23} Both the discrete and sliding window approach, however, have distinct advantages and disadvantages and are subject to active research in our laboratory. As calls for randomized clinical trials using HRC as a new vital sign accumulate,^{3,13,43} new challenges in data processing are emerging. Specifically, most of the currently available HRC and all frequency-domain techniques are jeopardized by presence of ectopic beats and other artifacts in the data. It is imperative that as we carry this research to clinical trials, we work together in multidisciplinary teams to take advantage of the automatic arrhythmia detection capabilities that exist in the cardiovascular device industry; to improve data capture, storage, compression, and transmission; and to incorporate these “new vital signs” into meaningful decision-support systems suitable for daily clinical use.

CONCLUSION

Several independent measures of complex variability in the heart rate decreased after combined TR/HS and were restored with resuscitation. These changes were independent of changes in traditional frequency-domain measures of heart-rate variability such as high frequency power. Heart rate complexity may be useful for diagnosis of TR/HS and for monitoring resuscitation.

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