Is heart period variability associated with the administration of lifesaving interventions in individual prehospital trauma patients with normal standard vital signs?*

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Objective: **To determine whether heart period variability provides added value in identifying the need for lifesaving interventions (LSI) in individual trauma patients with normal standard vital signs upon early medical assessment.**

Design: **Retrospective database review.**

Setting: **Helicopter transport to Level 1 trauma center and first 24 hrs of in-hospital care.**

Patients: **Prehospital trauma patients requiring helicopter transport to Level 1 trauma center.**

Measurements and Main Results: **Heart period variability was analyzed from electrocardiographic recordings collected from 159 prehospital trauma patients with normal standard vital signs (32 LSI patients, 127 No-LSI patients). Although 13 of the electrocardiogram derived metrics demonstrated simple (i.e., univariate) discrimination between groups, at the multivariate level, only fractal dimension by curve length (FD-L) was uniquely associated with group membership (LSI vs. No-LSI, $p = .0004$). Whereas the area under the receiver operating characteristics curve for FD-L was 0.70, the overall correct classification rate (true positives and true negatives) of 82% was only 2% higher than the baseline prediction rate of 80% (i.e., no information except for the known proportion of overall No-LSI cases, 127 of 159 patients). Furthermore, 84% of the individual FD-L values for the LSI group were within the range of the No-LSI group.**

Conclusions: **Only FD-L was uniquely able to distinguish patient groups based on mean values when standard vital signs were normal. However, the accuracy of FD-L in distinguishing between patients was only slightly better than the baseline prediction rate. There was also very high overlap of individual heart period variability values between groups, so many LSI patients could be incorrectly classified as not requiring an LSI if a single heart period variability value was used as a triage tool. Based on this analysis, heart period variability seems to have limited value for prediction of LSIs in prehospital trauma patients with normal standard vital signs. (Crit Care Med 2010; 38:1666–1673)**

KEY WORDS: R-R interval; heart rate; heart period variability; trauma; decision support; triage

In the prehospital setting, trauma patients are traditionally monitored and triaged using standard vital signs, including heart rate, blood pressure, arterial oxygen saturation, and radial pulse. However, with many traumatic injuries, these standard vital signs are well regulated by reflex compensatory mechanisms (e.g., increased sympathetic activation with hemorrhage) and so do not begin to change until late in the progression toward cardiovascular decompensation (1). By the time changes are detected in these parameters, it may be too late to intervene effectively and administer a lifesaving intervention (LSI). As a result, efforts have been devoted to identifying early indicators of physiologic deterioration for application in both the civilian and military trauma settings (1).

Although heart period variability has been recognized as a potential tool for monitoring the physiologic status of patients for >40 yrs (2), e.g., for noninvasive assessment of the autonomic compensatory responses (3), generalized acceptance and application of these monitoring techniques to the clinical setting has not occurred. Several studies (4–9) have demonstrated the potential utility of heart period variability as an indicator of mortality in intensive care unit patients many hours before death. Similarly, recent studies using data collected from prehospital trauma patients have demonstrated an association between heart period variability and the administration of LSIs (10, 11), injury severity (11), and eventual mortality (12–15). In these studies, however, at least one standard vital sign (e.g., Glasgow Coma Scale motor [GCSm] score) also distinguished the two groups of patients (e.g., LSI vs. No-LSI, Lived vs. Died), so the added value of heart period variability monitoring for decision support is unclear. In fact, a lower GCSm was independently associated with the eventual administration of an LSI in prehospital trauma patients (re-

***See also p. 1747.**

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ceiver operating characteristic [ROC] area under the curve of 0.800) (10); the area under the curve increased to 0.897 with addition of heart period variability metrics (10). However, we propose that the value of heart period variability depends on whether it can provide unique, reliable, and predictable information in individual patients who are compensating from their injuries and so have normal standard vital signs. This patient population is particularly vulnerable, as currently utilized techniques and technology in the prehospital setting are not sensitive enough to detect the true nature of their physiologic deterioration.

For heart period variability to be considered a reliable diagnostic tool, it must be reproducible from one time to the next under the same physiologic conditions, and it must be able to consistently distinguish the physiologic status of an individual patient (16–18). We (18) recently demonstrated that, on average, a wide range of heart period variability metrics tracked changes in stroke volume during progressive central hypovolemia in healthy human subjects ($r \geq .87$), but on an individual basis, the correlations across successive levels of hypovolemia were poor (range, $r = .0–.49$). Similarly, Tan et al (16) assessed both the reproducibility of fractal properties of heart period variability in individual research subjects and the ability of these metrics to reliably differentiate between autonomic blockade and a baseline control condition. In 50% of subjects, this index of heart period variability could not distinguish the two conditions at least half the time, despite marked differences in average group responses ($p < .001$ between conditions). These studies highlight the potential limitations of applying traditional statistics (such as comparing group means) to the clinical setting, as misleading conclusions could be made about the diagnostic utility of these data for the individual patient.

The aim of this study was to determine whether heart period variability metrics would be associated with the administration of subsequent LSIs in individual patients with normal standard vital signs. We hypothesized that, under these conditions, some metrics of heart period variability would reliably and predictably enable the distinction between prehospital trauma patients who received an LSI and patients who did not.

MATERIALS AND METHODS

Patient Selection

This study was approved by the Institutional Review Boards of the University of Texas Health Science Center, Houston, TX, and Brooke Army Medical Center, Fort Sam Houston, TX. Patients were selected from the U.S. Army Institute of Surgical Research Trauma Vitals database (1). This database contains trauma patient records collected during the prehospital transport phase to Memorial Hermann Hospital in Houston, TX (helicopter transport) and the Brooke Army Medical Center and the University of Texas Health Science Center in San Antonio, TX (helicopter or ground transport).

Data entered into the Trauma Vitals database were obtained from electronic records from onboard vital signs monitors and from standard run sheets completed by the attending paramedic, either during or after transportation of the patient to the emergency department. Heart rate (*via* continuous electrocardiogram [ECG]) and noninvasive blood pressure (every 3 mins *via* a brachial cuff) were recorded on the vital signs monitor, whereas Glasgow coma score (GCS—motor, verbal, and eye), radial pulse character, and capillary refill were manually assessed by the paramedic. These vital signs, age, sex, mechanism of injury, prehospital and in-hospital interventions, incident and transport times, and patient outcome (mortality) were entered into the database (1). An Excel spreadsheet was generated to include the deidentified data of all patients within the database. However, to ensure ECG signals were recorded at a frequency of >250 Hz (19), we assessed only the 700 patients with electronic vital sign data collected on a PIC-50 vital signs monitor (WelchAllyn, Buffalo Grove, IL).

From these 700 records, patients were down-selected based on the presence of normal standard vital signs defined as follows: 1) systolic blood pressure of ≥90 mm Hg; 2) GCSm of 6; 3) normal radial pulse; and 4) normal capillary refill (Fig. 1). The first valid blood pressure values obtained from the electronic data files collected and downloaded from the PIC-50 monitor were entered into the Excel spreadsheet for each patient.

A total of 245 patients had normal standard vital signs and a continuous ECG collected at 375 Hz on the PIC-50 vital signs monitor (Fig. 1). The ECG waveforms from each patient were imported into data analysis software (WinCPRS, Absolute Aliens, Turku, Finland), and R waves were automatically detected and marked at their occurrence in time. All ECG waveforms were then manually scanned to ensure accurate R-wave detection and to identify noise, ectopy, or aberrant beats. As subsequent heart period variability analyses required a minimum of 800 continuous R-R intervals (RRIs) without noise or interference (20), ECG records were discarded if they contained <800 RRIs (n = 29), contained electromechanical noise/interference (n = 3), or >0.5% of the ECG waveform contained ectopic beats (n =

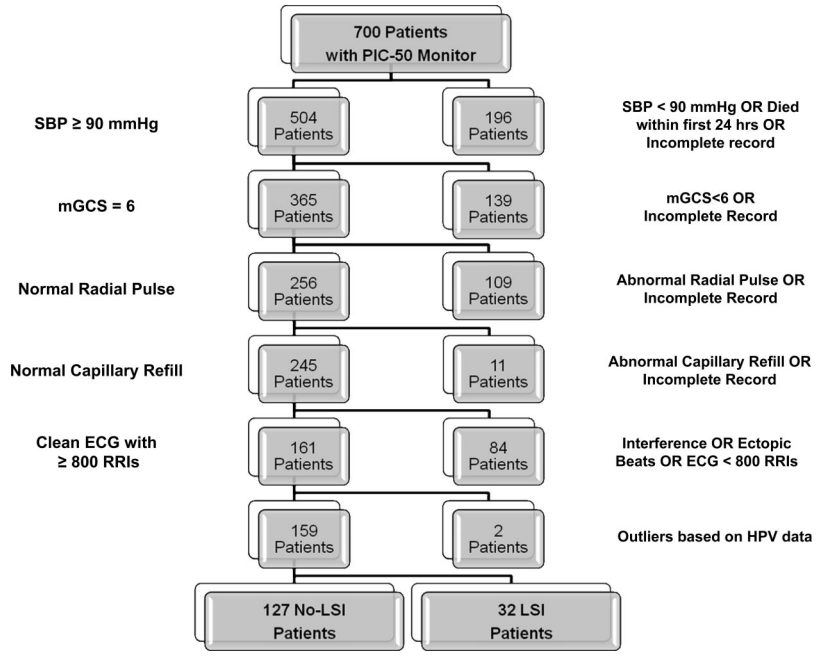


Figure 1. Flow chart describing the down-selection of patients based on normal standard vital signs and clean electrocardiographic signals, resulting in 127 No-lifesaving intervention (*LSI*) and 32 LSI patients. *SBP*, systolic blood pressure; *mGCS*, Glasgow Coma Scale motor; *ECG*, electrocardiogram; *RRIs*, R-R intervals; *HPV*, heart period variability.

52). In ECG records that contained <0.5% ectopic beats (n = 33), the aberrant beats were interpolated.

The remaining patients were further separated into patients who received a lifesaving intervention within 24 hrs of their injury (LSI) and patients who did not receive a lifesaving intervention (No-LSI). The list of LSIs included: intubation, chest tube, packed red blood cell transfusion, pericardiocentesis, cricothyrotomy, thoracotomy, angiography (with or without embolization), needle decompression, cardioversion, cardiopulmonary resuscitation, or surgical intervention, as previously defined (1, 21).

Data Analysis

Heart period variability measurements were made from the first available 800 RRI ECG recording that met the previously outlined criteria. The following metrics were selected for analysis, encompassing the time, frequency, and complexity domains (the definitions for these metrics are briefly outlined in Table 1):

- Time domain: RRI, heart rate, RRI SD, RRI root mean squared SD, Poincaré plot descriptors SD 1 and SD 2 and the ratio of SD 2/SD 1, complex demodulation low frequency, complex demodulation high frequency;
- Frequency domain: RRI low-frequency power, RRI high-frequency power;
- Complexity: Approximate entropy, sample entropy, Lempel-Ziv entropy, fractal dimensions by curve length (FD-L), fractal dimensions by dispersion analysis, stationarity, symbol dynamics entropy, forbidden words, detrended fluctuations analysis.

Statistical Analysis

Unpaired Student's *t* tests were used to determine the mean differences between the LSI and No-LSI patients for numerical vital sign data, and a chi-square test was used to compare the sex ratios and mechanism of injury between groups. Both univariate and multivariate logistic regression was used to predict group membership (i.e., LSI vs. No-LSI) from the ECG-derived metrics of heart period variability. Before analysis, the data were screened for out-of-range values and possible outlier observation *via* multivariate outlier analysis (i.e., Mahalanobis distances). When appropriate, data transformations (e.g., natural logs) were used to normalize skewed distributions. ROC curves were derived from the logistic prediction equations along with various measures of prediction accuracy (i.e., R squared, distributional overlap, false-negative prediction rate, LSI values included within the No-LSI range, and area under the ROC curve).

RESULTS

Two of the 161 patients were identified as outliers (>6 SD away from the multivariate normal distribution) and were excluded from further analysis (Fig. 1). Of the 32 patients who received an LSI, only three received a prehospital LSI (1 cardiopulmonary resuscitation, 1 chest tube, and 1 intubation). There was no record of these three patients receiving any other LSI within the first 24 hrs of medical care. Of the remaining 29 patients, 40 in-hospital LSIs were performed within the first 24 hrs of admission (12 blood transfusions, 2 intubations, 10 chest tubes and 16 surgical interventions). Nineteen patients received 1 LSI, 9 patients received 2 LSIs, and 1 patient received 3 LSIs. Patient characteristics and vital sign data are presented in Table 2. Both the LSI and No-LSI groups had a greater percentage of male patients

Table 1. Definition of each heart period variability metric of interest

Variable	Abbrev.	Units	Description
Time Domain			
R-R interval	RRI	ms	The time between each R wave
Heart rate	HR	beats/min	The number of times the heart beats within a 60-sec time period
RRI SD	RRISD	ms	The standard deviation of RRIs within a specified time
RRI root mean squared SD	RMSSD	ms	Root mean square difference among successive RRIs
Poincaré plot descriptor-SD 1	SD1	—	The standard deviation measuring the dispersion of points across the line of identity of a Poincare plot (28–30)
Poincaré plot descriptor-SD 2	SD2	—	The standard deviation measuring the dispersion of points along the line of identity of a Poincare plot (28–30)
Poincaré plot ratio	SD2/SD1	—	Ratio of SD2 to SD1
Complex demodulation LF	CDM LF	—	The amplitude of low-frequency oscillations in the RRI signal (31)
Complex demodulation HF	CDM HF	—	The amplitude of high-frequency oscillations in the RRI signal (31)
Frequency Domain			
RRI low-frequency power	LF	ms^2	Power spectral density of the low-frequency oscillations (0.04–0.15 Hz) of the RRI (3)
RRI high-frequency power	HF	ms^2	Power spectral density of the high-frequency oscillations (0.15–0.4 Hz) of the RRI (3)
Complexity			
Approximate entropy	ApEn	—	A measure of the regularity of the RRI signal; irregularity results in high ApEn, regularity results in low ApEn (32)
Sample entropy	SampEn	—	A measure of the regularity of the RRI signal, similar to ApEn but less dependent on record length (33)
Lempel-Ziv entropy	LZEn	—	A measure of the regularity or randomness of the RRI signal (20)
Fractal dimensions by curve length	FD-L	—	A measure of the fractal nature (self similarity) of the RRI signal. High FD-L indicates a more complex signal (20, 33, 34)
Fractal dimensions by dispersion analysis	FD-DA	—	A measure of the fractal nature (self-similarity) of the RRI signal. High FD-DA indicates a more complex signal (20, 33, 34)
Symbol dynamics entropy	SymDyn	—	A measure of the probability of particular patterns or sequences occurring within an RRI signal (20, 35)
Forbidden words	FW	%	The proportion of sequences that never or rarely occur in the RRI signal ($p < .1\%$) (20, 36)
Stationarity	StatAv	—	The stability of the RRI signal; the tendency of the mean and standard deviation to vary with time (38). Smaller values denote greater Stationarity of the signal (37)
Detrended fluctuations analysis	DFA	—	Determines long (DFA-L) and short (DFA-S) range correlations in the RRI signal (38)

than female patients. The LSI group was also younger ($p = .07$), had a greater percentage of penetrating injuries, a higher Injury Severity Score (ISS) ($p = .06$) and lower field eye GCS ($p = .04$), although the mean difference was only 0.1 points between groups.

Both the univariate and multivariate comparisons between the LSI and No-LSI groups are given in Table 3. Although 13 of the ECG-derived heart period variability metrics demonstrated simple (i.e., univariate) discrimination between groups, at the multivariate level only the FD-L was uniquely associated with group membership. Once the variance associated with FD-L was accounted for, no further discrimination between groups was obtained by inclusion of the other ECG-derived metrics (Table 3).

The ROC curve derived from the FD-L logistic regression is presented in Figure 2, along with the cross classification table of prediction accuracy. The area under the ROC curve equaled 70%. This area was primarily due to a shift in the curve as a result of a high false-negative rate (84%), coupled with the fact that there were only six predicted LSI events compared with 32 actual events. As can be seen from the ROC curve, the area is artificially inflated due to the fact that the curve does not originate at the origin. Although the false-positive rate was low (1%), the overall correct classification rate (82%) was only 2% greater than the baseline (i.e., no information except the proportion of overall No-LSI cases; 127 of 159 patients) prediction rate (80%).

Figure 3 presents side-by-side box plots comparing the two groups over FD-L values. The model R squared from the logistic regression was approximately 10%. This equates to a distributional overlap in the two FD-L group distributions of 58%. Furthermore, 84% of the FD-L values for the LSI group were within the range (1.53–1.93) of the No-LSI group.

These findings for FD-L were the best case scenario of the 13 metrics that distinguished the two groups with univariate analysis. The ranges for four additional metrics are presented in Figure 4 to demonstrate the similar overlapping distributions among the LSI and No-LSI patients for all investigated heart period variability metrics.

Table 2. Demographics and matched vital sign data for patients who received a lifesaving intervention (LSI) and patients who did not (No-LSI)

	LSI	No-LSI	*p*
Number of patients	32	127	—
Sex	9 F (28%); 23 M (72%)	50 F (39%); 77 M (61%)	.33
Age	34 ± 2	39 ± 1	.07
MOI	9 Penetrating (28%)	9 Penetrating (7%)	.002
	23 Blunt (72%)	111 Blunt (87%)	
	0 Unknown (0%)	7 Unknown (6%)	
ISS	17.3 ± 2.0	13.9 ± 0.8	.06
Capillary refill	Normal (<2 secs)	Normal (<2 secs)	Matched
Radial pulse	Normal	Normal	Matched
Field GCSm	6.0 ± 0.0	6.0 ± 0.0	Matched
Field GCSv	4.7 ± 0.09	4.8 ± 0.04	.51
Field GCSe	3.8 ± 0.08	3.9 ± 0.02	.04
Field GCS TOTAL	14.5 ± 0.2	14.7 ± 0.1	.15
Field SBP	131 ± 5	131 ± 2	.94
Field DBP	88 ± 3	90 ± 2	.62
Field PP	43 ± 4	41 ± 1	.57

MOI, mechanism of injury; ISS, Injury Severity Score; GCS, Glasgow Coma Score motor (m), verbal (v) and eye (e); SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; F, female; M, male.

Data are mean ± SE.

Table 3. Electrocardiographic-derived metrics of heart period variability for patients who received a lifesaving intervention (LSI) and patients who did not (No-LSI), using 800 R-R intervals of data

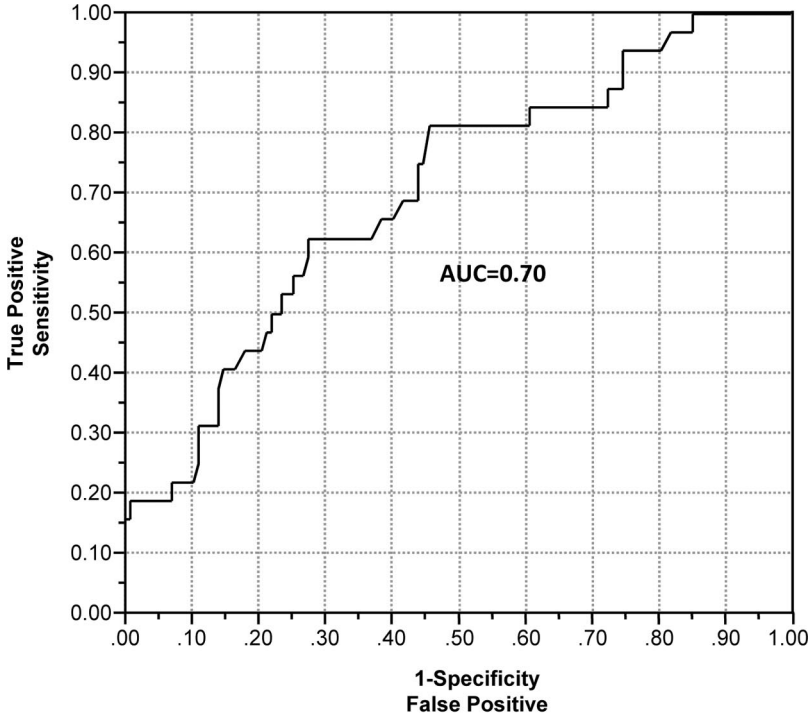
			p	
Variable	LSI (n = 32)	No-LSI (n = 127)	Univariate	Multivariate
RRI, ms	627 ± 29	661 ± 10	.50	.52
HR, bpm	101 ± 4	94 ± 1	.17	.98
RRISD, ms[a]	25.4 ± 2.8	28.9 ± 1.4	.50	.97
RMSSD, ms[a]	9.9 ± 1.4	13.7 ± 0.8	.02	.98
HF, ms^{2a}	51 ± 14	75 ± 9	.03	.97
LF, ms^{2a}	202 ± 51	269 ± 29	.05	.77
HF/LF[a]	0.22 ± 0.03	0.28 ± 0.02	.16	.28
CDM HF[a]	5.7 ± 0.9	7.9 ± 0.5	.02	.98
CDM LF[a]	12.6 ± 1.8	16.5 ± 0.9	.11	.88
SD1	7.1 ± 1.0	9.7 ± 0.6	.11	.55
SD2	35.0 ± 3.9	39.6 ± 1.9	.61	.90
SD2/SD1	6.1 ± 0.5	4.7 ± 0.2	.0007	.94
ApEn	1.01 ± 0.05	1.16 ± 0.02	.0005	.67
SampEn	1.02 ± 0.06	1.21 ± 0.02	.002	.93
LZEn	0.51 ± 0.03	0.60 ± 0.01	.002	.82
FD-L	1.65 ± 0.02	1.73 ± 0.01	.0001	.004
FD-DA	1.12 ± 0.01	1.15 ± 0.01	.36	.37
StatAv	0.86 ± 0.02	0.79 ± 0.01	.03	.54
SymDyn	0.60 ± 0.02	0.65 ± 0.01	.004	.74
% FW[b]	56 ± 2	50 ± 1	.03	.46
DFA short	1.33 ± 0.06	1.38 ± 0.02	.62	.80
DFA long	1.07 ± 0.04	0.95 ± 0.01	.02	.62

RRISD, R-R interval standard deviation; RMSSD, R-R interval root mean squared standard deviation; HF, high frequency; LF, low frequency; CDM, complex demodulation; ApEn, approximate entropy; SampEn, sample entropy; FD-L, fractal dimensions by curve length; FD-DA, fractal dimensions by dispersion analysis; StatAv, stationarity; SymDyn, symbol dynamics entropy; FW, forbidden words; DFA, detrended fluctuations analysis.

[a]Data transformations (e.g., natural logs) were used to normalize skewed distributions; [b]mean difference was opposite to the expected values from the literature (i.e., the LSI value is higher than the No-LSI value). Data are mean ± SE.

DISCUSSION

Over recent years, there has been growing interest in the potential utility of ECG-derived heart period variability metrics for clinical decision support in the prehospital setting (10–15, 22). In each of these studies, various metrics of heart period variability were associated with a significant clinical outcome, specifically, the administration of an LSI (10, 11) or mortality (12–15). However, in each of these studies, the patient populations were also separated by significant differ-



		Actual Group: LSI	Actual Group: No-LSI	
Predicted Group	LSI	5	1	(6)
	No-LSI	27	126	(153)
		(32)	(127)	

Figure 2. Receiver operating characteristic curve for fractal dimension by curve length, and associated contingency table of prediction accuracy. *LSI*, lifesaving intervention.

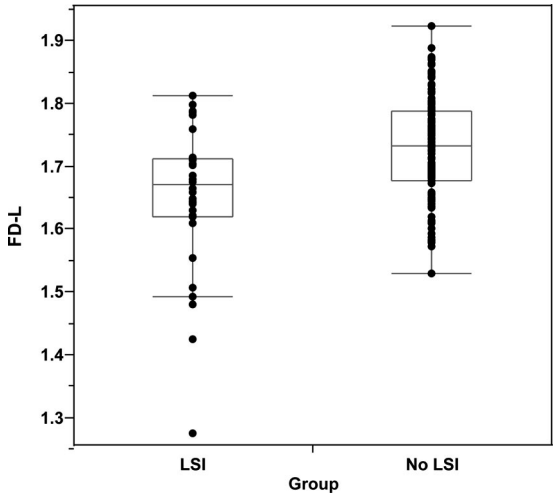


Figure 3. Box-and-whisker plot of fractal dimension by curve length (*FD-L*) demonstrating the high degree of overlap of individual values between the lifesaving intervention (*LSI)* (n = 32) and No-LSI patients (n = 127). Of individual LSI patient values, 84% fall within the No-LSI range.

ences in injury severity, identified by GCS (motor and total) obtained in the field, and ISS, which is retrospectively calculated at the time of hospital discharge or patient death. In these cases, a simple field assessment of injury severity effectively provided equivalent discrimination between the patient groups as computationally complicated heart period variability calculations from the ECG (e.g., ROC area under the curves, GCS = 0.800 vs. GCS and heart period variability = 0.897) (10). Additionally, the assessment of manual vital signs alone (i.e., radial pulse, motor GCS, and verbal GCS) in prehospital trauma patients yielded even higher discriminatory power (ROC area under the curve = 0.969) for the eventual administration of a field LSI (23).

The most vulnerable patients, however, are those with intact autonomically mediated reflex responses who are adequately compensating for their injuries so standard vital signs are not altered from "normal." These patients were the target population for analysis in the current investigation. We were able to replicate the findings of a previous study (10) with statistically significant differences in the mean values between LSI and No-LSI patients in some heart period variability metrics. Of the nine common metrics investigated in these two studies, five showed consistent differences across both studies, whereas the remaining four metrics were not statistically distinguishable in the current study. This disparity may reflect the higher severity of injury and mortality within the LSI group of the previous study (field GCSm = 3.4 ± 0.4; mortality = 15%) (10) compared with the current study (field GCSm = 6.0 ± 0.0; mortality = 0%), resulting in greater separation between the LSI and No-LSI patients. However, upon more detailed analysis, we found that even in the one metric (FD-L) that was uniquely associated with group membership, 84% of individual heart period variability values in the LSI patients crossed over into the range of the No-LSI patients. Furthermore, as 80% of the patients in this cohort did not require an LSI, clinicians choosing not to administer an LSI to any of the 159 patients would be as accurate as using heart period variability to inform their decision (overall accuracy of FD-L was 82%). Under circumstances where standard vital signs are normal and injury severity (ascertained from the field GCSm) is matched among patients, metrics of heart period variability did not provide the discriminatory power necessary for distinguishing patients requiring an LSI on an individual basis.

Although the use of ECG waveform complexity (i.e., FD-L) information for the prediction of future LSI comes with a high false-negative rate (0.84), it did catch five patients who would otherwise receive no

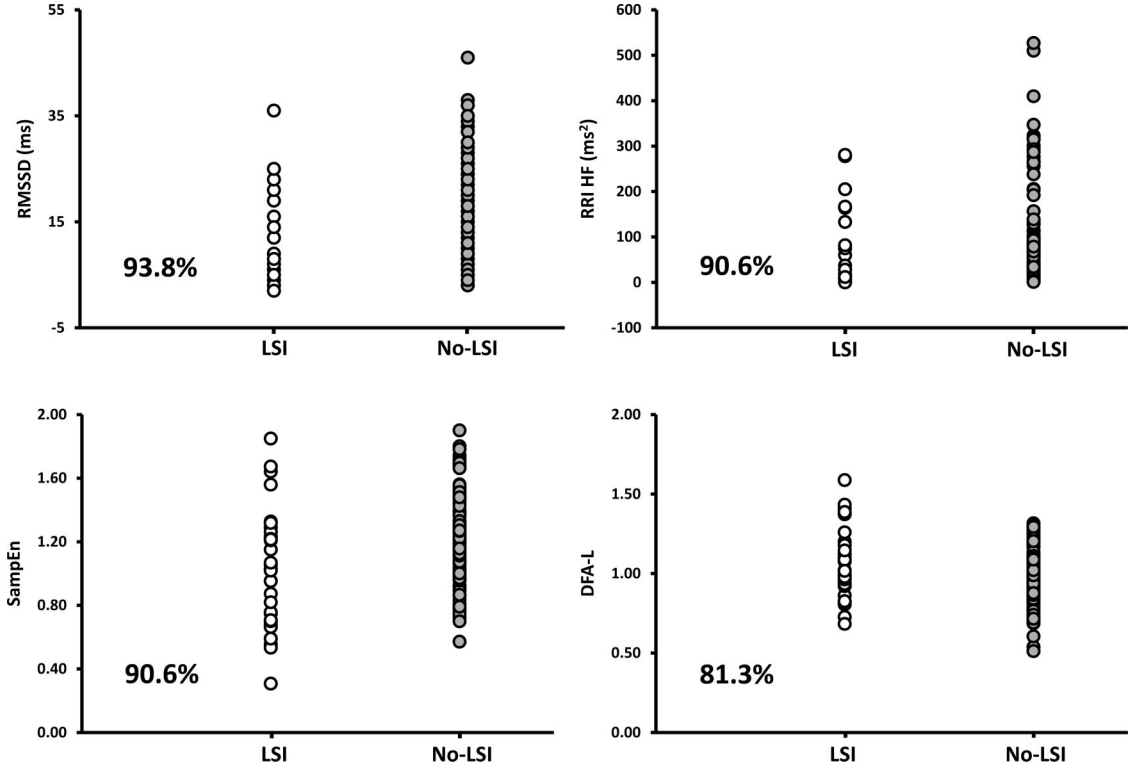


Figure 4. Individual values of four representative heart period variability metrics for lifesaving intervention (*LSI*) (n = 32) and No-LSI (n = 127) patient groups (each point represents a single patient). The percentage of individual LSI patient values that fall within the range of the No-LSI group are presented in each plot. *RMSSD*, R-R intervals root mean squared standard deviation; *RRIHF*, R-R intervals high frequency; *SampEn*, sample entropy; *DFA-L*, detrended fluctuations analysis–long range correlations.

special attention. In the face of otherwise normal vital signs, information from FD-L may be advantageous when FD-L values are very low (<1.5) (Fig. 2). At the same time, however, 27 patients would not be receiving medical attention when it was actually required. It should also be noted that these error rates are conservative since they were determined on the same data that derived the statistical model. If the prediction were applied to new data, the error rates are likely to increase.

The findings of this investigation highlight the limitations of using traditional inferential statistical analyses alone (e.g., group means) for application of research findings to the clinical setting. Although these analyses can provide some insight about underlying physiologic responses to the experimental or clinical intervention (18), recent investigations (16, 18) have drawn attention to the potential risk of masking individual responses by only presenting group means. Tan et al (16) assessed the individual variability of fractal components of heart period variability and the ability of this metric to consistently distinguish between a baseline control condition and complete autonomic blockade, both in the supine and up-right tilt positions across repeated experimental days. Based on group means, the measurement of detrended fluctuations analysis–long range correlations was able to distinguish the supine from tilt positions during the control condition and autonomic blockade from the control condition in the supine position (16). However, the mean differences were not consistent across the three separate experimental days, nor were they repeatable among individual subjects; in 50% of subjects for at least one comparison, fractal components of heart period variability was not able to distinguish the control condition from complete autonomic blockade (16). Although the data were not presented, the authors (16) mentioned that an identical assessment of sample entropy and approximate entropy yielded results that were qualitatively similar to the analysis of fractal components of heart period variability.

To better understand the diagnostic capabilities of heart period variability for the detection of hemorrhage, our laboratory (18) recently assessed the ability of a wide range of metrics to track progressive reductions in stroke volume *via* application of lower body negative pressure in healthy human subjects. Again, whereas group mean data provided promising results with high aggregate correlations between heart period variability metrics and stroke volume ($r \geq .87$), subject level correlations across successive levels of hypovolemia were poor (range, $r = .0–.49$) (18). Furthermore, the wide interindividual variability of many of these metrics, even in resting healthy human subjects (17), makes it difficult to determine the physiologic state of an individual patient. For example, in our recent lower body negative pressure study (18), the value of sample entropy in one subject at baseline (sample entropy = 1.27) was identical to the value of another subject who had experienced a 67% reduction in stroke volume with experimentally induced central hypovolemia (sample entropy = 1.27). Similarly, the range of heart period variability values in the LSI patient population studied in this investigation crosses over into the range from a group of healthy human subjects (e.g., 21% crossover for FD-L, 45% crossover for sample entropy) studied in our laboratory (17); i.e., some trauma patients requiring aero-medical evacuation to a

Level 1 trauma center cannot be distinguished from healthy, resting research subjects based on a single measurement of heart period variability. Although a single "snapshot" measurement is unlikely to provide the necessary sensitivity or specificity for clinical decision making, the findings in our laboratory study (18) also indicated that trending measurements of heart period variability over time will provide little added value to the clinician. The issue of individual reliability is particularly important when the findings of research investigations are to be applied to the clinical setting, where the individual patient will be assessed without reference to group averages. Under these conditions, the intervention or mode of monitoring should be reliable and predictable at the individual level, and hence provide added value to clinical decision making in the majority of cases. The above-mentioned studies demonstrate that these requirements are not achieved with heart period variability.

The utility of a diagnostic tool not only depends on the sensitivity of the measurement but also on the specificity; i.e., whether it can reliably distinguish one physiologic condition from another. Mathematically, many metrics of heart period variability will decrease purely as a consequence of an increase in heart rate (24), regardless of the stimulus. This relationship has important practical implications as heart rate can increase not only from an underlying traumatic injury and associated pain but also due to other stimuli potentially associated with the trauma setting, such as anxiety, dehydration, heat or cold stress, and physical activity/movement (25). Under these conditions, assessment of heart period variability without consideration of other confounding factors may result in a false-positive alert to medical personnel, particularly if all other standard vital signs seem normal. As such, heart period variability lacks the specificity to injury required for diagnostic utility in the prehospital trauma setting.

It should be noted that many of the heart period variability metrics assessed in this investigation were highly correlated with each other and were, therefore, redundant once the "unique" information was obtained from FD-L. This redundancy is not surprising because these calculations are all derived from the same RRI time series and explains why differences seen between the LSI and No-LSI patients using univariate analysis disappears when examined multivariately. The issue of redundancy was also apparent in the study by Cancio et al (10), where only two of 13 heart period variability metrics were independently associated with the administration of an LSI.

Limitations

The nature of the prehospital trauma setting lends itself to a number of unavoidable limitations for retrospective research studies. Although patients were separated into two groups based on the administration of an LSI, it is unclear whether each LSI was actually required, based on physiologic indicators, or if they were given as part of a standard protocol. Because accurate identification of the conditions that dictated LSI administration could not be assessed from our database, and for consistency with other studies assessing the association of vital signs and heart period variability with the administration of LSIs (10), we have included all patients with all LSIs received with the first 24 hrs. Similarly, although we selected patients based on the documented administration of LSIs, it is possible that some of the No-LSI patients actually received an LSI but it was not documented in the patient notes. Consequently, in this and other studies, this type of analysis cannot provide a prediction of whether an LSI was required, but rather indicates an association with the administration of an LSI.

Although the time of LSI administration was usually documented in the database, these times are often recalled by the flight paramedic after delivery of the patient to the emergency department, so it may not represent the precise time of intervention. Consequently, in the three patients who received prehospital LSIs, it is unclear whether these were administered before or after the collection of the ECG segment used for analysis. This limitation does not apply to the remaining 29 LSI patients, as their interventions were administered in the hospital, after the analyzed ECG segment was recorded.

Not all physiologic variables that can be utilized for decision support in the prehospital setting were available for analysis (e.g., respiratory rate and respiration quality). Similarly, real time assessment of patient status would include the observation of multiple measurements over time. The nature of this prehospital trauma database, however, did not facilitate the inclusion of this type of data.

Accurate assessment of heart period variability requires clean ECG segments, free from interference and ectopy (19). In the current investigation, we excluded 34% of patients with normal standard vital signs due to interference, ectopy (>0.5% of the waveform) or inadequate ECG length (<800 RRIs), consistent with previous studies on prehospital trauma patients where between 42% and 74% of patient records were excluded (10, 12, 14). Exclusion of such a large percentage of patients from analysis may introduce selection bias into the results (19, 26) and also questions the utility of these measurements for prehospital patient monitoring.

The patients selected for inclusion in this study represent a narrow subset of the total trauma patient population. Utilizing patients with more severe penetrating injuries and/or battlefield trauma patients would likely yield greater separation of individual heart period variability values. Indeed, in studies by Cooke et al (15) and Batchinsky et al (14), heart period variability distinguished patients who lived from those who died, and those patients who died had average ISSs of >30. However, in these studies some standard vital signs were also different between patient groups. Our intention in the current study was to assess whether heart period variability could provide added value to the clinician when all currently utilized measures of patient status seem "normal." It seems likely that these normal standard vital signs are associated with less severe injuries, hence lower ISSs. The one preliminary study (27) performed on battlefield trauma patients to date presented individual heart period variability data for 11 patients and showed that each of the four patients who received an LSI had heart period variability values (*via* point correlation dimension, PD2i) below a certain threshold, whereas all of the No-LSI patient data were above the threshold. However, complete vital signs and ISSs were not included in this brief abstract, so it is not clear if these also distinguished the LSI and No-LSI patients, or if the battlefield injuries were more severe than injuries in civilian patients (*via* GCS or ISS values). More patients and more details on the clinical status of these patients are required for an accurate assessment of these findings.

CONCLUSIONS

In a cohort of prehospital trauma patients with normal standard vital signs, measures of heart period variability were able to distinguish patients who received an

LSI from those who did not, based on mean responses between groups. However, there was also very high overlap of individual heart period variability values between groups, so many LSI patients could be incorrectly classified as not requiring an LSI if a single heart period variability value was used as a triage tool. Application of heart period variability to the clinical setting is also limited by poor inter- and intraindividual reproducibility, the exclusion of a large percentage of patient data due to ectopy and interference in the ECG waveform, and the lack of specificity to a particular injury modality. As a consequence of these significant practical issues, our results provide the first systematic evidence that heart period variability metrics may have limited value for prediction of LSIs in prehospital trauma patients with normal standard vital signs.

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