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Real-time sample entropy predicts life-saving interventions after the Boston Marathon bombing☆

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ABSTRACT

Purpose: Identifying patients in need of a life-saving intervention (LSI) during a mass casualty event is a priority. We hypothesized that real-time, instantaneous sample entropy (SampEn) could predict the need for LSI in the Boston Marathon bombing victims.
Materials and methods: Severely injured Boston Marathon bombing victims (n = 10) had sample entropy (SampEn) recorded upon presentation using a continuous 200-beat rolling average in real time. Treating clinicians were blinded to real-time results. The correlation between SampEn, injury severity, number, and type of LSI was examined.
Results: Victims were males (60%) with a mean age of 39.1 years. Injuries involved lower extremities (50.0%), head and neck (24.2%), or upper extremities (9.7%). Sample entropy negatively correlated with Injury Severity Score ($r = -0.70$; $P = .023$), number of injuries ($r = -0.70$; $P = .026$), and the number and need for LSI ($r = -0.82$; $P = .004$). Sample entropy was reduced under a variety of conditions.

	SampEn (mean ± SD)	*P*
Amputation, n = 5	0.7 ± 0.3	
No amputation, n = 5	1.9 ± 0.8	.027
Transfusion, n = 5	0.7 ± 0.3	
No transfusion, n = 5	1.9 ± 0.8	.027
Intubation, n = 6	0.8 ± 0.3	
No intubation, n = 4	2.1 ± 0.7	.027
Vasopressors, n = 7	0.8 ± 0.3	
No vasopressors, n = 3	2.4 ± 0.3	.004

Conclusions: Sample entropy strongly correlates with injury severity and predicts LSI after blast injuries sustained in the Boston Marathon bombings. Sample entropy may be a useful triage tool after blast injury.
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1. Background

Appropriate triage of patients after traumatic injury remains a challenge, especially during mass casualty events, such as the Boston Marathon bombing on April 15, 2013. Despite the large number of victims, not all would be severely injured or require life-saving interventions (LSI). Traditional vital signs may not become altered until compensatory physiologic mechanisms become completely exhausted [1]. Various measures of heart rate variability (HRV) and complexity have been shown to be superior to vital signs at predicting mortality after trauma [2,3]. Reduced irregularity or loss of complexity due to traumatic injury has been previously been associated with increased need of prehospital LSI and mortality [1,4]. Of note, these studies have all required prospective data collection with off-line, retrospective data analysis (or manually verified R wave detection), consequently making real-time analysis impossible.

The aim of this study was to prospectively evaluate the use of a real-time measure of heart rate complexity as a potential triage tool during the tragic events of the Boston Marathon bombing. We hypothesized that real-time, instantaneous heart rate complexity could predict the need for LSI in the Boston Marathon bombing victims.

2. Methods

The Massachusetts General Hospital is an academic level 1 trauma center managed by an unchanging dedicated trauma and acute care surgery team. Patients that met criteria for trauma team activation

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and sustained extensive blast injuries during the Boston Marathon bombing on April 15, 2013, were prospectively enrolled in the study. Bombing patients were enrolled in this study under an existing institutional review board–approved investigation with waiver of informed consent.

After arrival to the trauma resuscitation bay during the discovery phase of care, research staff performed a single 10-minute electrocardiogram recording with an ICON Noninvasive Cardiac Monitor (Osypka Medical, La Jolla, CA) that had been modified and programmed to calculate, display, and record HRV (SD of the normal-to-normal R-R interval [SDNN]) and heart rate complexity (sample entropy [SampEn]) in real time. Continuous measurements of SV and CO were also determined by electrical impedance cardiography. To calculate SampEn, recordings of 200 consecutive beats in a continuous sliding-window fashion was used, as previously described by Batchinsky et al [5]. For SampEn calculations, the dimension parameter m was 2, and the filter parameter r was 20% of the SD. SD of the normal-to-normal R-R interval measurement was determined using previously described time-domain analysis [2-4].

All trauma activation patients from the bombing, without exclusion, were included in the analysis. Treating clinicians were blinded to the real-time study results. Demographic data including age, sex, Injury Severity Score (ISS), Glasgow Coma Scale (GCS), hematocrit (Hct), and hemoglobin (Hb), number and type of injuries, vital signs on admission and before surgery, blood products, and all surgical procedures were recorded and entered into an Excel spreadsheet (Microsoft Excel 2003, Redmond, WA).

The primary outcome was need for emergent LSI. *Life-saving intervention* was defined as urgent and elective therapeutic measures that were needed to sustain the life of the blast victims such as any emergent surgical procedure, blood transfusion, intubation, administration of vasopressors, and cardiopulmonary resuscitation (CPR).

Descriptive data are reported as means and SDs, medians, and interquartile ranges or as frequencies (%) as appropriate. Pearson and Spearman correlation coefficients were used to summarize the relationship between heart rate complexity (HRC) and other continuous variables. Two-sample *t* tests were used to compare the mean HRC between those with and without each LSI. SAS version 9.3 (The SAS Institute, Cary, NC) and GraphPad Prism 5.0 (GraphPad Software, San Diego, CA) were used for the statistical analysis. A 2-sided $P < .05$ was considered statistically significant.

3. Results

From the large number of patients who presented to our institution immediately after the Boston Marathon bombing, only 10 (n = 10) of the victims met trauma team activation criteria. All trauma team activation patients were admitted due to extensive injuries caused by the explosion. All 10 patients had SDNN and SampEn successfully recorded. Most of the victims were young male individuals (60%) with a mean age of 39.1 years (presenting demographics, Table 1). Despite the relatively stable hemodynamic parameters on admission (systolic blood pressure, 116.9 ± 54.8 mm Hg; heart rate, 96.7 ± 22.7 beats per minute), all of the patients had multiple injuries affecting several body parts (ISS, 13.0 ± 8.0). After the initial triage, resuscitation, and index damage control surgery, the patients were admitted to the appropriate services according to their injury pattern and required therapy: trauma and emergency surgery (80%, n = 8) and orthopedic surgery (20%, n = 2).

All of the victims required at least 1 operation with a median time from admission to first surgery of 54 minutes (range, 24-1320). One patient received successful CPR twice due to pulseless electrical activity—once on the way to the operating room and a second time shortly before the beginning of the surgical procedure. Overall, the median blood loss during the initial surgical procedure was 250 mL. However, 2 of the victims lost more than 4500 mL during their index operation. On average, patients received 6.1 ± 7.6 U packed red blood cells, 4.0 ± 8.0 U fresh frozen plasma, and 4.7 ± 9.2 U of platelets during the total hospital stay.

The scope of injuries is described in Table 2. The most common injuries involved the lower extremities (50.0%, n = 26), the head and neck (24.2%, n = 15), or the upper extremities (9.7 %, n = 6). Of note, although 24% of patients had head and neck injuries, no patient had an intracranial lesion; all injuries were extracranial soft tissue injuries. Burns constituted 29.0% of the injuries. All the patients required at least 1 LSI (Table 3). The most common LSIs were emergent surgery (100%), use of vasopressors (70%), and endotracheal intubation (60%). Although completion amputation was the fourth most common LSI, half of the patients lost at least 1 limb after the bombing. The median hospital length of stay was 13.5 days (8.0-18.0), and the intensive care unit (ICU) stay was 3 days (0-8). No patients died.

Patient age negatively correlated with the mean SampEn ($r = -0.73$; $P = .016$) (Table 4). In addition, a positive association was observed between patient blood pressure on admission and SampEn ($r = 0.66$; $P = .039$). On the contrary, higher number of injuries ($r = -0.70$; $P = .026$) and injury burden (ISS) was associated with low SampEn ($r = -0.70$; $P = .023$). Similarly, a strong negative correlation was observed between the number LSI performed and the mean SampEn ($r = -0.82$; $P = .004$). When comparing mean

Table 1
Patient demographics

Characteristic	Blast victims (n = 10)
Age (y), mean ± SD	39.1 ± 15.4
Sex	
Male, n (%)	6 (60 %)
Female, n (%)	4 (40 %)
ISS, mean ± SD	13.0 ± 8.0
GCS on arrival, mean ± SD	14.4 ± 0.8
Hct on arrival (%), mean ± SD	35.8 ± 8.6
Hb on arrival (g/L), mean ± SD	12.0 ± 2.8
Sys BP on arrival, mean ± SD	116.9 ± 54.8
HR on arrival, mean ± SD	96.7 ± 22.7
Sys BP before surgery, mean ± SD	121.2 ± 28.0
HR before surgery, mean ± SD	89.0 ± 24.0
Blood loss (ml), median (Q1 - Q3)	250.0 (200–400)
PRBC total, mean ± SD	6.1 ± 7.6
FFP total, mean ± SD	4.0 ± 8.0
Platelet total, mean ± SD	4.7 ± 9.2
Surgical service	
Trauma and emergency surgery, n (%)	8 (80 %)
Orthopedic surgery, n (%)	2 (20%)
Time from admission to first surgery (min), median (Q1-Q3)	54.0 (46.0-1028.0)

Sys BP indicates systolic blood pressure; PRBC, packed red blood cells; FFP, fresh frozen plasma.

Table 2
Description of injuries

Characteristic	Blast victims (n = 10)	
	Specific injuries, mean ± SD	Specific injuries, n (%)
Head and neck	1.5 ± 1.4	15 (24.2%)
Thorax	0.1 ± 0.3	1 (1.6%)
Heart	0.1 ± 0.3	1 (1.6%)
Major vessels	0.3 ± 0.7	3 (4.8%)
Perineum	0.1 ± 0.3	1 (1.6%)
Abdomen/abdominal wall	0.4 ± 0.5	4 (6.5%)
Upper extremities	0.6 ± 0.5	6 (9.7%)
Lower extremities	3.1 ± 2.0	31 (50.0%)
Total number of injuries	6.2 ± 3.6	62 (100%)
Total number of burn injuries	1.8 ± 1.9	18 (29.0%)
Percentage burns all degrees (%)	14.6 ± 16.1	/
Percentage burns second and third degree (%)	5.4 ± 7.9	/

Table 3
Description of outcomes

Characteristic	Blast victims (n = 10)
No.of LSI per patient, median (Q1-Q3)	4.0 (1.0-5.0)
LSI	
Amputations, n (%)	5 (14.7 %)
Blood transfusions, n (%)	5 (14.7 %)
Intubation, n (%)	6 (17.6 %)
Vasopressors, n (%)	7 (20.6 %)
CPR, n (%)	1 (2.9 %)
Surgery, n (%)	10 (29.4 %)
Total number of LSI	34 (100%)
HOS LOS, median (Q1-Q3)	13.5 (8.0-18.0)
ICU LOS, median (Q1-Q3)	3.0 (0.0-8.0)
Mortality, n (%)	0 (0 %)

HOS LOS indicates hospital length of stay; ICU LOS, intensive care unit length of stay.

Table 5
The association between HRC and the LSIs

Characteristics blast victims (n = 10)	HRC	*P*
Service		
Trauma and emergency surgery, mean ± SD	1.0 ± 0.7	.012
Orthopedic surgery, mean ± SD	2.3 ± 0.4	
Amputations, mean ± SD	0.7 ± 0.3	.027
Without amputations, mean ± SD	1.9 ± 0.8	
Blood transfusion, mean ± SD	0.7 ± 0.3	.027
Without blood transfusion, mean ± SD	1.9 ± 0.8	
Intubation, mean ± SD	0.8 ± 0.3	.027
Without intubation, mean ± SD	2.1 ± 0.7	
Vasopressors, mean ± SD	0.8 ± 0.3	.004
Without vasopressors, mean ± SD	2.4 ± 0.3	
CPR, mean ± SD	1.2	.73
Without CPR, mean ± SD	1.3 ± 0.9	

SampEn between those with and without a specific LSI (Table 5), patients who had amputations, received blood transfusions, were intubated, or received vasoactive agents had a nearly 50% reduction in SampEn. SD of the normal-to-normal R-R interval was not predictive of LSI or ISS in this patient population.

4. Discussion

This report supports the results of previously published studies showing the reproducibility and reliability of heart rate complexity measures in predicting the need of LSIs [1,4,6]. Specifically, SampEn predicted LSI and was correlated with ISS in the victims of the Boston Marathon bombing presenting to our institution as trauma team activation patients.

Heart rate variability is generally considered to be a nonspecific indicator of health, mirroring the reaction plasticity of the autonomic nervous system. Loss of variability or regularization of the heart rate is believed to be a global index of poor health [7]. In addition, reduced HRV is thought to indicate cardiac uncoupling and to be associated with mortality and deteriorating physiologic reserve in trauma ICU patients [2]. Heart rate complexity is a specific approach used to analyze the heart rate time series by quantifying the amount of irregularity or randomness of the signal. We then correlate this irregularity with clinically significant events in the hope of detecting occult conditions that require immediate or near-immediate intervention. Sample entropy, a specific approach to heart rate complexity analysis, measures the likelihood of finding similar patterns in the signal so that lower values correspond to increased regularity and decreased complexity of the signal. The alterations in SampEn are based on the activity of the autonomous nervous system, the vagal cardiac control, and the sympathetic cardiac stimulus, among a host of other neurohumoral inputs that are poorly described.

Sample entropy was used in this analysis of 3 main reasons: SampEn has shown to be a reliable predictor of poor outcome [1,4,5], and SampEn has been shown to predict mortality with very short data sets [4,5], and an existing SampEn study protocol was already in place at the time of the Boston Marathon bombing on April 15, 2013.

Advanced age is thought to be associated with decreased physiologic reserve and ability of the autonomous nervous system to react to stress. Our results suggest that advanced age negatively correlates with SampEn shortly after blast injury ($r = -0.73$; $P =$ .016). Possible explanations could be existing comorbidities or use of medications that negatively influence cardiac responsiveness [8,9]. However, none of the patients in the cohort had any known cardiac disease or received β-blockers, calcium-channel blockers, or other cardioactive pharmaceuticals 24 hours before or during the SampEn measurement.

Two negative correlations strongly support the use of SampEn as a potential reliable triage tool: ISS ($r = -0.70$; $P = .023$) and number of LSI ($r = -0.82$; $P = .0004$). Based on these results, a single SampEn measurement, performed early after admission, could provide significant additional predictive information. It is notable that the traditional vital signs of the bombing patients were with normal limits (systolic blood pressure on admission, 116.9 ± 54.8 mm Hg; heart rate on admission, 96.7 ± 22.7 beats per minute; GCS on admission, 14.4 ± 0.8). The City of Boston and our institution specifically had enough resources to manage every bombing patient optimally; however, one can imagine circumstances where resources may become overwhelmed and predictive information about LSIs may become invaluable. When investigating the association between the different LSI and SampEn, we noted that patients, whose limbs were amputated, were intubated, received blood transfusions or vasopressors, had an approximately 50% reduction in SampEn (Table 5). Our results support the proposed SampEn cutoff value of 1.1 previously suggested by our group [10], although a much larger population needs to be studied before firmly establishing a threshold for triage. In this limited series, only 1 patient had SampEn greater than 1.1 who required at least 1 LSI.

Table 4
Correlations between HRC, descriptive variables, and outcomes

Characteristics Blast Victims (N = 10)	Pearson correlation with HRC	*P*	Spearman correlation with HRC	*P*
Age	−0.73	.016	−0.85	.002
Hct on admission	0.61	.063	0.54	.110
Sys BP on admission	0.66	.039	0.72	.019
HR on admission	−0.26	.460	−0.13	.712
GCS on admission	0.55	.101	0.57	.087
ISS	−0.70	.023	−0.69	.027
No. of total injuries	−0.70	.026	−0.72	.019
Head and neck	−0.78	.008	−0.84	.002
Thorax	−0.38	.281	−0.47	.174
Heart	−0.25	.485	−0.29	.413
Major vessels	−0.47	.168	−0.58	.080
Perineum	−0.25	.485	−0.29	.413
Abdomen/ abdominal wall	−0.15	.688	−0.29	.423
Upper extremities	−0.27	.449	−0.29	.423
Lower extremities	−0.11	.763	−0.03	.945
No. of total burned areas	−0.03	.934	0.03	.938
Sys BP preoperative	0.28	.429	0.20	.577
HR preoperative	−0.30	.398	−0.06	.880
Blood loss during first surgery	−0.29	.452	−0.26	.507
Total PRBC	−0.62	.054	−0.66	.037
Total FFP	−0.41	.238	−0.49	.153
Total platelets	−0.28	.429	−0.41	.246
No. of LSI	−0.82	.004	−0.69	.026
No. of surgeries	−0.32	.367	−0.20	.582
HOS LOS	−0.38	.274	−0.20	.587
ICU LOS	−0.76	.011	−0.83	.003

The study has several limitations that need to be addressed. The small sample size (n = 10) is an obvious limitation and one attributable to our single-institution experience after the bombings. To our knowledge, no other trauma receiving center in the city that treated Boston Marathon bombing patients recorded HRV or complexity data. In addition, only trauma activation bombing patients were recorded. The "walking wounded" who were treated and released within 24 hours were not recorded. Another limitation is the time of recording. Because some of the patients were intubated or had received opiates at time of the recordings, it is still not clear how anesthesia and analgesics would influence HRV and complexity.

In conclusion, SampEn strongly correlates with injury severity and predicts LSI after blast injuries sustained in the Boston Marathon bombings. Sample entropy may be a useful triage tool after blast injury.

References

[1] Cancio LC, Batchinsky AI, Salinas J, Kuusela T, Convertino VA, Wade CE, et al. Heart-rate complexity for prediction of prehospital lifesaving interventions in trauma patients. J Trauma 2008;65(4):813–9.

[2] Morris Jr JA, Norris PR, Ozdas A, Waitman LR, Harrell Jr FE, Williams AE, et al. Reduced heart rate variability: an indicator of cardiac uncoupling and diminished physiologic reserve in 1,425 trauma patients. J Trauma 2006 Jun;60(6):1165–73 [discussion 1173–4].

[3] Mejaddam AY, van dW, Chang Y, Cropano CM, Sideris AC, Hwabejire JO, et al. Development of a rugged handheld device for real-time analysis of heart rate: entropy in critically ill patients. J Spec Oper Med 2013;13(1):29–33.

[4] Batchinsky AI, Cancio LC, Salinas J, Kuusela T, Cooke WH, Wang JJ, et al. Prehospital loss of R-to-R interval complexity is associated with mortality in trauma patients. J Trauma 2007;63(3):512–8.

[5] Batchinsky AI, Salinas J, Kuusela T, Necsoiu C, Jones J, Cancio LC. Rapid prediction of trauma patient survival by analysis of heart rate complexity: impact of reducing data set size. Shock 2009;32(6):565–71.

[6] Proctor KG, Atapattu SA, Duncan RC. Heart rate variability index in trauma patients. J Trauma 2007 Jul;63(1):33–43.

[7] Norris PR, Anderson SM, Jenkins JM, Williams AE, Morris Jr JA. Heart rate multiscale entropy at three hours predicts hospital mortality in 3,154 trauma patients. Shock 2008;30(1):17–22.

[8] Maule S, Rabbia F, Perni V, Tosello F, Bisbocci D, Mulatero P, et al. Prolonged QT interval and reduced heart rate variability in patients with uncomplicated essential hypertension. Hypertens Res 2008;31(11):2003–10.

[9] Ko SH, Song KH, Park SA, Kim SR, Cha BY, Son HY, et al. Cardiovascular autonomic dysfunction predicts acute ischaemic stroke in patients with type 2 diabetes mellitus: a 7-year follow-up study. Diabet Med 2008;25(10):1171–7.

[10] Mejaddam AY, et al. Real-time heart rate complexity on hospital arrival predicts the need for life-saving interventions in trauma activation patients. J Trauma 2013;75(4):607–12.