Exercise-Induced Changes in Compensatory Reserve and Heart Rate Complexity

Michelle B. Mulder; Sarah A. Eidelson; Mark D. Buzzelli; Kirby R. Gross; Andriy I. Batchinsky; Victor A. Convertino; Carl I. Schulman; Nicholas Namias; Kenneth G. Proctor

BACKGROUND: Portable noninvasive Heart Rate Complexity (HRC) and Compensatory Reserve Measurement (CRM) monitors have been developed to triage supine combat casualties. Neither monitor has been tested in upright individuals during physical exercise. This study tests the hypothesis that exercise evokes proportional changes in HRC and CRM.

METHODS: Two instruments monitored volunteers (9 civilian and 11 soldiers) from the Army Trauma Training Department (ATTD) before, during, and following physical exercise. One recorded heart rate (HR, bpm), cardiac output (CO, $L \cdot min^{-1}$), heart rate variability (HRV, root mean square of successive differences, ms), and HRC (Sample Entropy, unitless). The other recorded HR, pulse oximetry (S_pO_2, %), and CRM (%).

RESULTS: Baseline HR, CO, HRV, HRC, and CRM averaged 72 $\pm$ 1 bpm, 5.6 $\pm$ 1.2 $L \cdot min^{-1}$, 48 $\pm$ 24 ms, 1.9 $\pm$ 0.5, and 85 $\pm$ 10% in seated individuals. Exercise evoked peak HR and CO at $>$ 200% of baseline, while HRC and CRM were simultaneously decreased to minimums that were $\leq$ 50% of baseline (all $P < 0.001$). HRV changes were variable and unreliable. S_pO_2 remained consistently above 95%. During a 60 min recovery, HR and CRM returned to baseline on parallel tracks ($t^{1/2}$=11 $\pm$ 8 and 18 $\pm$ 14 min), whereas HRC recovery was slower than either CRM or HR ($t^{1/2}$=40 $\pm$ 18 min, both $P < 0.05$).

DISCUSSION: Exercise evoked qualitatively similar changes in CRM and HRC. CRM recovered incrementally faster than HRC, suggesting that vasodilation, muscle pump, and respiration compensate faster than cardiac autonomic control in young, healthy volunteers. Both HRC and CRM appear to provide reliable, objective, and noninvasive metrics of human performance in upright exercising individuals.

KEYWORDS: heart rate variability, homeostasis, compensatory reserve measurement, heart rate complexity.

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Humans can respond to major blood loss, exercise, or other pathophysiologic stress with little change in most vital signs until the point of decompensation.[17] Each individual has a slightly different tolerance before decompensation because slightly different metabolic and neuroendocrine responses are mobilized to restore homeostasis.[7] Changes in heart rate variability (HRV) are among the most widely-studied responses to stress. A search for this topic in PubMed in June 2019 yielded over 24,000 publications. Nevertheless, routine clinical application of HRV has been limited because there is no standardized way to measure HRV, no uniform units or definitions of normal values, or even a consensus on the minimum time required to obtain an accurate, specific, and precise signal. In fact, currently there are over 25 separate and distinct methods to measure HRV, and most require either prolonged data collections and/or offline signal processing.[29] Recently the United States Army Institute of Surgical Research (USAISR) developed simple algorithms and a portable, noninvasive, real time monitor for a variable closely related to HRV.[1,6,21] Heart rate complexity (HRC) is calculated from the "complexity," or

From the Dewitt Daughtry Department of Surgery Divisions of Trauma, Burns, & Surgical Critical Care, University of Miami Miller School of Medicine and Ryder Trauma Center, Miami, FL.

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Address correspondence to: Kenneth G. Proctor, PhD, Professor of Surgery, Divisions of Trauma and Surgical Critical Care, Daughtry Family Department of Surgery, University of Miami Miller School of Medicine, Ryder Trauma Center, 1800 NW 10th Avenue, Suite 215, Miami, FL 33136; kproctor@miami.edu.

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entropy, of a series of 200 heart beats.[1] Recently, we described HRC changes during predeployment training activities of U.S. Army Forward Surgical Teams (FST) at the Army Trauma Training Department (ATTD) at the University of Miami.[24]

Every physiologic feedback mechanism (e.g., tachycardia, vasoconstriction, tachypnea) has a finite maximal ability to compensate to any pathophysiologic stressor; this finite "reserve" to maintain homeostasis can be defined by the difference between the maximal response and baseline steady state. Using this principle, the USAISR recently developed a portable, noninvasive monitor incorporating a Compensatory Reserve Measurement (CRM) for trauma triage.[13,34] Self-learning algorithms derived from ejection and reflected photoplethysmography waveforms estimate how well tissue perfusion and oxygen delivery are maintained by compensatory mechanisms.[12,31,32] A CRM estimate is produced after the first 30 heart beats, followed by a new CRM estimate after each subsequent beat, and normalized to a 0–100% scale. In unanesthetized volunteers with stepwise removal and replacement of 20% blood volume, CRM accurately trends the progression from normovolemia to decompensation and back to normovolemia and is sensitive to the differing risks associated with differing tolerance to volume loss.[22] In trauma patients, CRM is a better predictor of the requirement for hemorrhage associated life-saving intervention (i.e., operation or angiography, local or tourniquet control of external bleeding, and transfusion) than traditional vital signs.[18]

HRC and CRM have separately shown superiority compared to traditional vital signs for trauma triage in supine individuals,[2,19,23] but they have never been compared side by side in the same patient or during milder physiologic stress, such as that associated with physical exercise in upright individuals. We hypothesized that HRC and CRM compensatory changes were proportional after physical exercise.

METHODS

Subjects

This study population was a convenience sample of volunteer civilians and soldiers at the ATTD from 2017–2018. Exclusion criteria were subjects with chronic medical conditions or those receiving chronic medications that alter cardiovascular function, but none met these criteria. Basic demographic information (age, gender, number of previous deployments, rank/military job description, weight, and height) were collected.

Equipment and/or Materials

This prospective observational study was approved by the University of Miami Institutional Review Board with informed consent. A Cooperative Research and Development Agreement was established with the USAISR for providing the CRM devices. Osypka Medical provided ICON Cardiometer instruments with embedded research modules computing HRC (https://www.osypkamed.com).

Procedure

Seven variables were simultaneously recorded using the two noninvasive monitors for about 90 min in seated or standing individuals engaged in physical activity. In most previous studies using either CRM or HRC, the monitored subjects were supine and motionless. In this study, the subjects were all seated for baseline measurements, then upright and moving for the remainder of the monitoring period. In a pilot study, we observed minimal differences in CRM and HRC caused by postural changes.

ICON data were collected using four surface EKG electrodes and a proprietary method termed "electrical cardiometry" which estimates stroke volume and other hemodynamic parameters from measurements of thoracic electrical bioimpedance.[5] CO is calculated from the product of stroke volume and HR. HRV is calculated from the root mean square of successive standard deviations (RMSSD) of normal sinus beats. HRC is calculated using a sample entropy algorithm developed at USAISR based on an established principle.[28] EKG electrodes were placed overlying the left carotid artery and in the left subcostal mid axillary line and hardwired to the portable monitor. Data were digitized every half second and downloaded after each trial into a text file with a unique time stamp. For a typical response, approximately 600–1000 separate measurements were averaged for each individual data point during a recording period.

The CRM device measured HR and CRM via a standard oximetry sensor (PureLight model 8000AA, Nonin Medical Inc., Plymouth, MN) on the middle finger connected to a portable pocket monitor. Nail deformities, discolorations and polish were accounted and adjusted for to maintain uniformity among participants. CRM was calculated using a proprietary, machine-learning algorithm [scaled 0–100% (0 = cardiovascular decompensation, 100% = normovolemia)][4,16] developed at USAISR that detects changes in photoplethysmography waveforms. Data were digitized every 5 s with a unique time/date stamp. Data from all subjects were stored into the memory cache then downloaded into a text file using proprietary software at USAISR. For a typical response, approximately 100–200 individual measurements were averaged for each data point during a recording period.

After a 5–10 min post instrumentation stabilization, a 5–10 min baseline was acquired in the sitting position. This was followed by an 8-flight stair ascent/descent at maximal exertion for 5–10 min, and then 60 min of monitored recovery during which participants resumed routine daily activities.

Statistical Analysis

SPSS version 24.0 (https://www.ibm.com/products/spss-statistics) was used. Parametric data are reported as mean ± SD and compared with Student's *t*-tests. Nonparametric data are reported as median (interquartile range 25–75%) and compared with Mann-Whitney *U*-test. Significance was assessed at $P \leq 0.05$.

RESULTS

The study population was comprised of 20 volunteers (9 civilian, 11 soldiers) at the ATTD. Mean (± SD) demographic data were 31 ± 10 yr of age, 72 ± 13 kg, 80% male, and included 5 surgeons, 6 medical students, 4 nurses, 2 OR techs, 1 combat medic, 1 physician assistant, and 1 administrator.

Fig. 1 and **Fig. 2** illustrate the individual variability in raw unfiltered data from seven simultaneously measured variables in two different soldiers before, during and for 60 min after exercise. The left panel shows changes in the four ICON variables and the right panel shows corresponding changes in the three variables measured on the CRM device. Fig. 1 shows data from a 32-yr-old female 66T OR RN weighing 59 kg and Fig. 2 shows data from a 23-yr-old male 68C LPN weighing 77.1 kg. HR increased from 70–80 bpm during a 5 min baseline to a peak after < 10 min of exercise to 140–160 bpm. The peak HR corresponded with peak cardiac output and minimum HRV, HRC, and CRM within each individual. After the exercise, all the variables gradually returned to the pre-exercise baseline, but the rate of return and the absolute values differed between and within individuals.

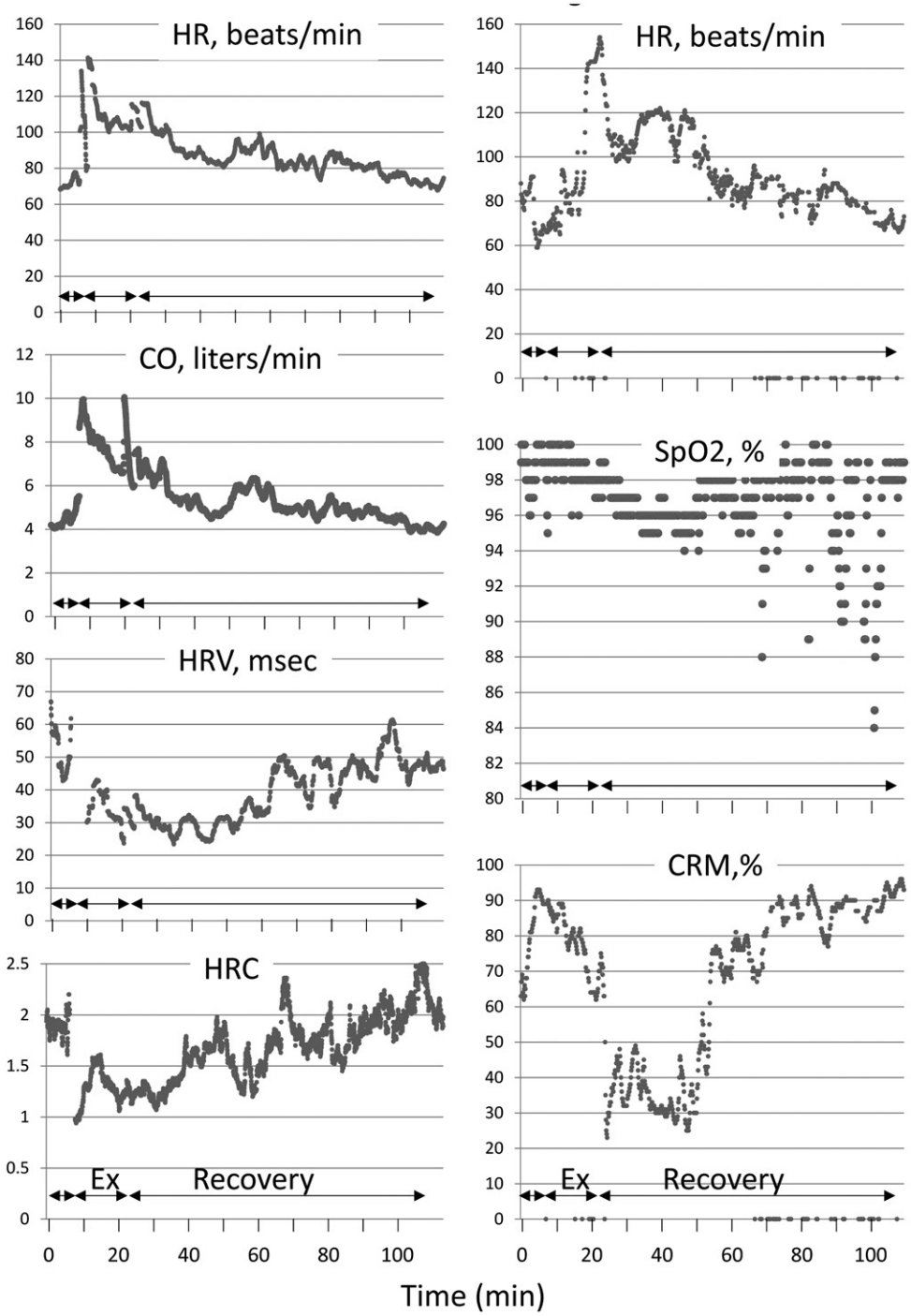

Fig. 1. Raw ICON (left panel) and CRM (right panel) data before, during, and for 60 min after exercise in one female soldier. The arrows indicate the baseline, exercise, and recovery periods.

Fig. 3 shows the population average HR, CO, HRC, and CRM values in baseline conditions as 68 ± 10 bpm, 5.0 ± 0.8 L · min^{-1}, 2.1 ± 0.5, and 85 ± 10%, respectively. During the first few minutes of exercise, HR and CO rose to an average of 106 ± 16 bpm (t = 11.30, df = 18) and 8.5 ± 1.5 L · min^{-1} (t = 11.61, df = 18) and then peaked at 154 ± 16 bpm (t = 19.32, df = 18) and 13.4 ± 2.7 L · min^{-1} (t = 15.09, df = 18), while HRC and CRM simultaneously decreased to a minima of 0.69 ± 0.44 (t = −9.44, df = 18) and 42 ± 12% (t = −13.69, df = 18) (all paired t-tests, $P < 0.001$). Meanwhile, S_pO_2 remained relatively constant. The average values at the end of recovery returned to near baseline for all variables

Although HRV data (measured via RMSSD) appeared reliable in some individuals, in several others, the signal was confounded by noise and movement and required tedious manual editing. For these reasons, HRV data were not presented. The overall average baseline HRV was 54 ± 28 ms (range 18–134 ms), which was not statistically distinguishable from the average HRV of 48 ± 24 ms (range 15–108 ms, t = 1.77, df = 18, P = 0.09) during exercise. The minimum value during exercise was 30 ± 19 ms (range 6–71 ms, t = −3.80, df = 18, P = 0.003 vs. baseline), but HRV failed to

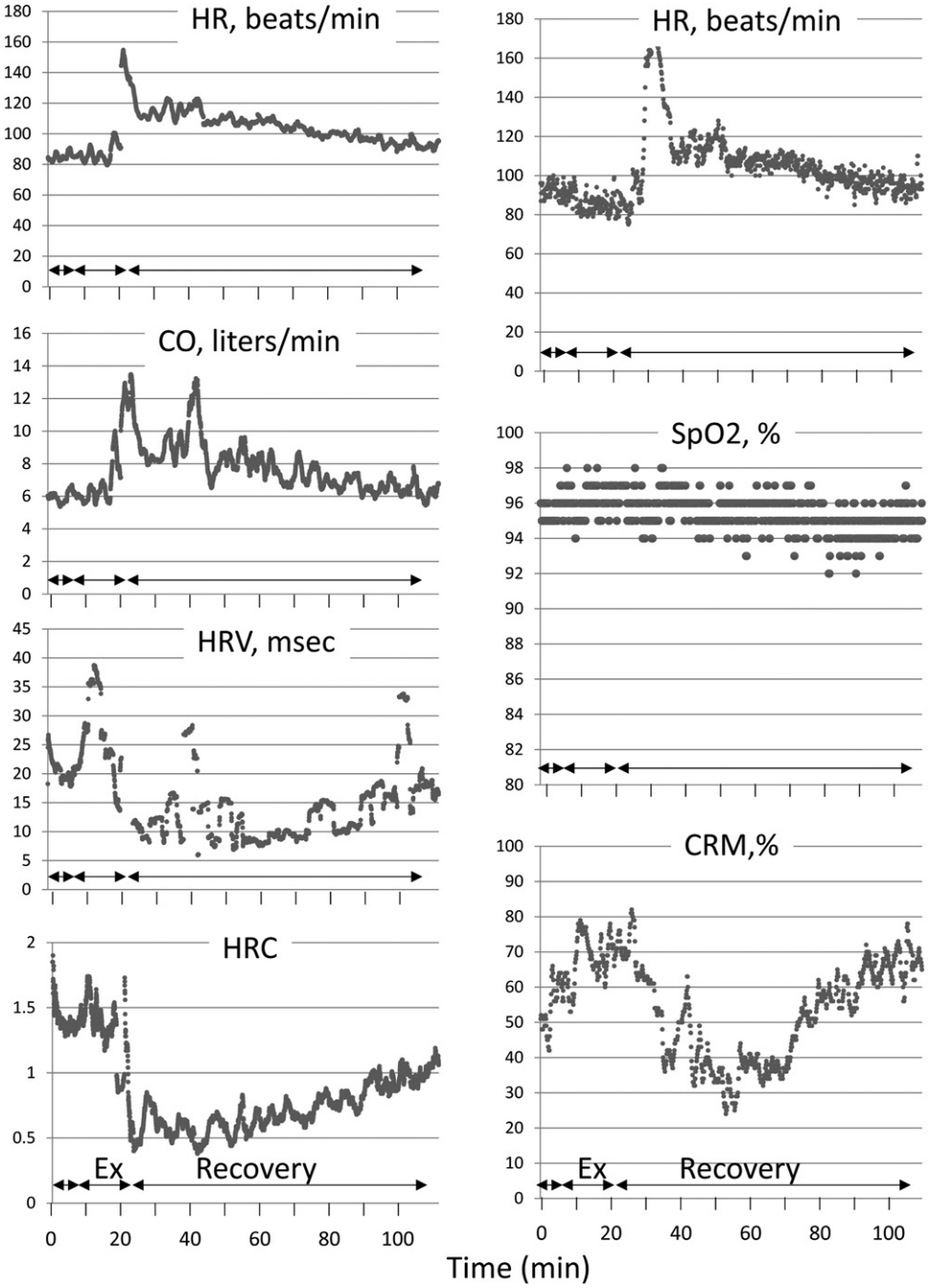

Fig. 2. Raw ICON (left panel) and CRM (right panel) data before, during, and for 60 min after exercise in one male soldier. The arrows indicate the baseline, exercise, and recovery periods.

recover after 60 min. At the end of observation, the value remained 31 ± 19 ms.

Fig. 4 shows the time-related recovery for the data measured by the ICON device (left panel) and the CRM device (right panel) on the same % baseline scale. The left panel shows HR peaked during exercise at 233 ± 41% of baseline, then rapidly recovered with a $t^{1/2} = 12 \pm 11$ min. CO showed a similar pattern to HR (data not shown). The right panel shows that HR peak (240 ± 36%) and recovery ($t^{1/2} = 9 \pm 6$ min) were virtually identical to the ICON. Average S_pO_2 remained consistently above 95% (data not shown). CRM reached a minimum of 51 ± 15% of baseline, and its recovery essentially tracked HR ($t^{1/2} = 18 \pm 14$ min). In contrast, HRC reached a minimum of 34 ± 23% of baseline, but its recovery was slower than either HR ($t = 6.24$, df = 18) or CRM ($t = 4.55$, df = 18) with a $t^{1/2}$ of 41 ± 17 min (both paired t, $P < 0.001$).

DISCUSSION

The results showed that exercise evoked qualitatively similar changes in CRM and HRC in both phase and magnitude. Whereas HRV-related variables are among the most widely studied feedback systems in biology, CRM is a relatively novel concept that integrates the sum total of all compensatory mechanisms based on feature extraction analysis of the ejection wave (all mechanisms that control the heart) and reflected wave (all mechanisms that control the vasculature). Since HRC reflects cardiac autonomic input, some association between HRC and CRM should be expected, particularly during an exercise stress in which autonomic control of the heart is a major compensatory mechanism. Autonomic control of the heart alters the arterial waveform and that is integrated in the CRM algorithm.[11] The faster time course for CRM recovery compared to HRC suggests that compensatory mechanisms other than cardiac autonomic control (e.g., vasodilation, muscle pump, respiration) are critical to rapid recovery from physical exercise.

It is well recognized that intense exercise is associated with a pronounced 'relative' hypovolemia due to vasodilation in the working muscles and skin.[10] Additionally, an acute exercise stimulus that elicits maximal heart rates in humans (i.e., > 200 bpm), similar to those observed in the present investigation, causes an 'absolute' hypovolemia that can reduce plasma volume by as much as 12% in the upright posture.[9] The most likely mechanism underlying the reduction in plasma volume is an exercise-evoked increase in systemic arterial pressure which increases capillary hydrostatic pressure, which promotes fluid shifts from the vascular space to the

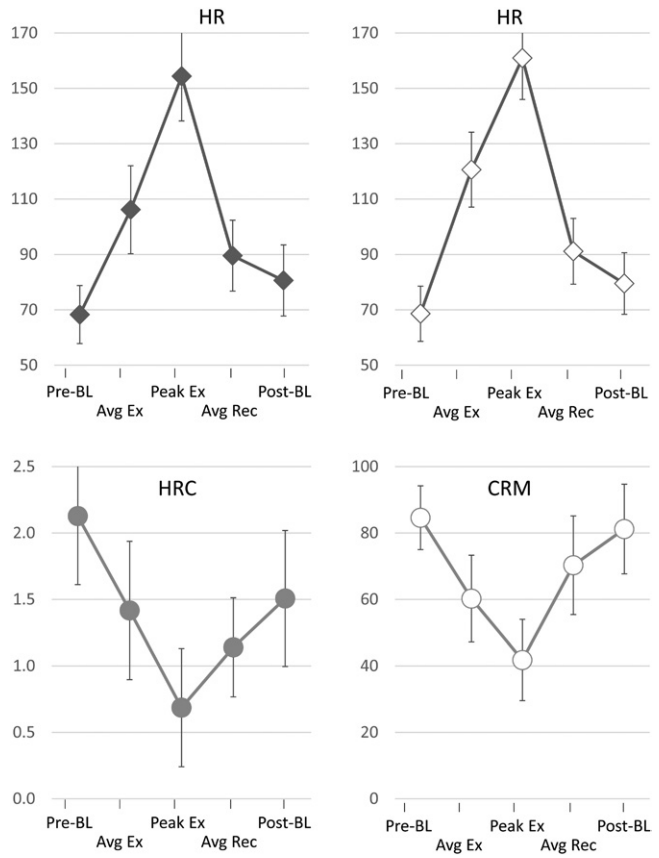

Fig. 3. Average HR and HRC (left panel) and HR and CRM (right panel) data before, during, and after exercise. All values are paired. Pre-BL = steady state baseline before exercise; avg ex = average during exercise (rising part of the biphasic response); peak ex = maximum (or minimum) during exercise; avg rec = average during recovery (falling part of biphasic response); post-BL = average value after 55–60 min of recovery. The avg ex, peak ex, and avg rec values for each variable were all significantly different than the pre- or post-BL (all $P < 0.05$).

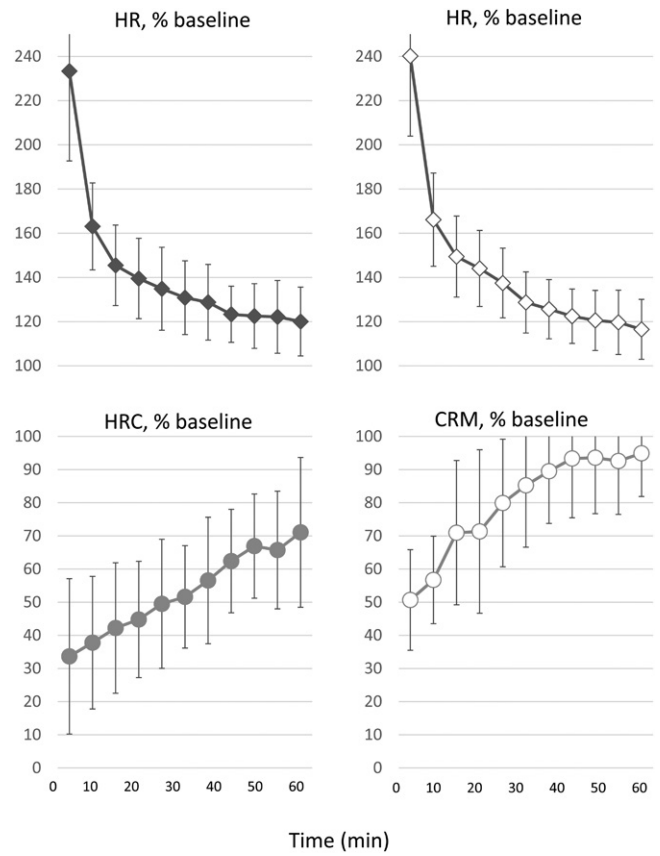

Fig. 4. Recovery of HR and HRC from one monitor and HR and CRM from the other monitor for 60 min after exercise as a function of time. All values are paired and are expressed relative to the pre-exercise steady state baseline. During each 5 min increment, in each individual, an average of 400 HR and HRC data points, and 70 HR and CRM data points were averaged to get one value per variable per time increment per individual. The population mean ± SD was obtained from these values. For the ICON cardiometer, the HR at ED_{50} was 167 ± 20% and the $t^{1/2}$ was 12 ± 11 min; the paired HRC at ED_{50} was 67 ± 12% and the $t^{1/2}$ was 41 ± 17 min ($P < 0.05$ vs. paired HR $t^{1/2}$). For the other device, the HR at ED_{50} was 170 ± 18% and the $t^{1/2}$ was 9 ± 6 min (neither of these values was different than the corresponding paired ICON values); the paired CRM at ED_{50} was 68 ± 8% and the $t^{1/2}$ was 18 ± 14 min ($P < 0.05$ vs. paired ICON value).

interstitium.[8] The combination of both relative and absolute hypovolemia caused by intense exercise contributes to a physiological stress that was reflected by qualitatively similar reductions in HRC and CRM (Fig. 3).

This study showed that physical exercise evoked peaks in HR and CO that were synchronized with reductions in both HRC and CRM. Another unique result emanating from the present study was the different recovery time courses of CRM and HRC. While tachycardia rapidly resolved in almost an exact parallel with CRM during recovery, HRC recovered significantly slower (Fig. 4). These findings suggest that compensatory mechanisms other than cardiac autonomic control (e.g., vasodilation, muscle pump, respiration) are critical to rapid recovery from physical exercise.

Fig. 1 and Fig. 2 illustrate noisy raw signals from two soldiers typical of those experienced during the extreme movement of intense physical exercise. The time to peak and magnitude of the tachycardia response differ slightly between the ICON and CRM monitor, but that was expected because the former technology triggers off the EKG while the latter triggers off a pulse oximeter, with both being sensitive to motion artifacts. Despite individual subject variability, the population data from the two devices were remarkably similar (Fig. 3). In most previous studies that employed either HRC or CRM, the monitored subjects were all supine. In the present study, the monitored subjects were seated during baseline data collection, but then standing upright and/or moving vigorously for the rest of the monitoring period.

HRV has been widely studied for more than 80 yrs. It is defined by the fluctuating time between normal sinus beats (RR intervals) and indicates modulation of the sinoatrial node by the autonomic nervous system. Afferent inputs from sensory and baroreceptors within the heart and great vessels, respiratory changes, vasomotor regulation, the thermoregulatory system, and alterations in endocrine function determine autonomic influence on the heart.[29] It is superior to traditional vital signs and trauma criteria in predicting the need for prehospital[20] or inhospital[30] life-saving interventions. There is accumulating evidence that burnout and stress-related dysregulation of the autonomic nervous system and the hypothalamic pituitary adrenal

axis are risk factors for cardiovascular disease and that these changes can be detected by measuring HRV. In one study,[14] 55 patients (34 men and 21 women) with burnout on sickness absence and 40 healthy participants (16 men and 24 women) were exposed to a psychosocial stressor consisting of mental arithmetic and public speech. In male burnout patients, baseline systolic blood pressure was higher, whereas basal alpha-amylase and cortisol reactivity were lower than in healthy men.[14] In female burnout patients, basal cortisol was lower compared to healthy women. However, reduced basal HRV and increased CO were observed in both male and female patients.[14] Unfortunately, routine HRV monitoring in many clinical situations is often confounded by several logistic issues when using time domain or frequency domain analysis.[29]

HRV and HRC are closely related and the two terms are often used as synonyms but in fact "complexity" is qualitatively and quantitatively distinguishable from traditional concepts and metrics of variability.[15] Complex variability is indeed synonymous with complexity, and things that exhibit complexity also exhibit variability, but not everything that varies exhibits complexity.[15] HRC reflects the overall disorder or randomness in the EKG signal by quantifying the probability of a repetitive pattern in the RR interval. If the next pattern can be predicted from the previous section, the signal is considered low in entropy and is therefore less complex.[29] HRC is exempt from many of the HRV logistic limitations, and in fact has been found to be superior to HRV in correlating to clinical outcomes following critical illness and trauma.[3,26,27] HRC correlates with physical conditioning[33] and is an independent predictor for the need for lifesaving interventions in trauma patients.[25] In any case, in this present study, HRC signals were more consistent, and less subject to artifact and noise, than simultaneously measured HRV in these vigorously exercising individuals.

There are several limitations of this study. First, these findings simply provide basic proof of concept that HRC and CRM, which have previously been validated as trauma triage tools in supine individuals, can also be used as noninvasive, reproducible and quantifiable markers of other forms of autonomic stress or human performance in upright and/or moving individuals. Further investigations are necessary to establish sensitivity and specificity and to correlate HRC and CRM with alternative metrics of physiologic stress or human performance. Second, some data were excluded for a variety of logistic reasons, such as short monitoring times due to battery life or memory malfunctions, movement artifacts in the unfiltered electrical signals, probes that fell off perspiring skin, wires of probes that interfered with movement, occasional sudden data drops, and/or failures in data downloads. When this occurred, the measurement was repeated so that all the variables were paired. Third, the small sample size of 20 volunteers may have contributed to type II errors. There may have been selection bias secondary to voluntary participation since the study population was comprised of physically fit, relatively young, healthy volunteers who may not have been representative of the general population. Finally, at present, the only FDA approved interface for the CRM device is the finger, and this restricts hand motion. This problem can be addressed with new probes that derive the CRM algorithm from other plethysmographic signals, such as the chest, wrist or earlobe.

CRM was first described in 2013 by Convertino et al.,[23] and there have been multiple validation studies in a variety of conditions since that time. Overall, these data report that CRM is among the earliest and most accurate metrics for identifying hypovolemia, with superior sensitivity, specificity and accuracy compared to traditional metrics. In fact, CRM outperformed systolic blood pressure in predicting the need for clinical interventions in trauma patients with hemorrhage,[19] was superior at detecting decompensation to metabolic measurements, superior to stroke volume as a predictor of cardiovascular decompensation, superior to traditional vital signs in detecting changes in blood volume following transfusion, and superior to peripheral perfusion index and pulse pressure variability in predicting decompensation with volume shifts caused by lower body negative pressure.[4,16] The results of this present investigation demonstrate the usefulness of the CRM, relative to HRC, to evaluate recovery from physical exercise. As such, our findings portend the usefulness for field unit commanders to assess the readiness status of their military and/or civilian personnel during repeated operational missions that otherwise might increase the risk of compromised health and safety.

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Authors and affiliations: Michelle B. Mulder, M.D., Sarah A. Eidelson, M.D., Carl I. Schulman, M.D., MSPH, Ph.D., Nicholas Namias, M.D., and Kenneth G. Proctor, Ph.D., Dewitt Daughtry Department of Surgery, Divisions of Trauma, Burns, & Surgical Critical Care, University of Miami Miller School of Medicine and Ryder Trauma Center, Miami, FL; Mark D. Buzzelli, M.D., Kirby R. Gross, M.D., and Kenneth G. Proctor, U.S. Army Trauma Training Department, Ryder Trauma Center and University of Miami Miller School of Medicine, Miami, FL;

Andriy I. Batchinsky, M.D., and Victor A. Convertino, Ph.D., Extracorporeal Life Support Capability Area, Battlefield Health & Trauma Center for Human Integrative Physiology, U.S. Army Institute of Surgical Research, JBSA Ft. Sam Houston, TX; and Andriy I. Batchinsky, The Geneva Foundation, Tacoma, WA.

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