The Matching of Sinus Arrhythmia to Respiration: Are Trauma Patients without Serious Injury Comparable to Healthy Laboratory Subjects?

Xiaoxiao Chen, Andrew T. Reisner, Liangyou Chen, Shwetha Edla, and Jaques Reifman

Abstract— **We sought to better understand the physiology underlying the metrics of heart rate variability (HRV) in trauma patients without serious injury, compared to healthy laboratory controls. In trauma patients without serious injury (110 subjects, 470 2-min data segments), we studied the correlation between sinus arrhythmia (SA) rate, heart rate (HR), and respiratory rate (RR). Most segments with $2.4 \leq HR/RR < 4.8$ exhibited SA-RR matching, whereas rate matching was absent in 81% of the segments with $HR/RR < 2.4$ and in 86% of the segments with $HR/RR \geq 4.8$. The findings were comparable, in some cases remarkably so, to previous reports from healthy laboratory subjects. The presence (or absence) of SA-RR matching, when SA is largely controlled by respiration, can be anticipated in this trauma population. This work provides a valuable step towards the definition of patterns of HRV found in trauma patients with and without life-threatening injury.**

I. Introduction

We sought to better understand the physiology that underlies metrics of heart rate variability (HRV). Respiration is a predominant determinant of HRV. Hence it has been argued that it is crucial to consider the relationship between HRV and respiration when interpreting HRV data [1]. In some circumstances, the frequency of sinus rhythm variation (sinus arrhythmia [SA]; rhythmic fluctuations in heart rate [HR]) is *wholly* driven by the respiratory rate (RR), such that their rates will be identical [2-5]. The amplitude of SA is also correlated, inversely, to RR [3]. Rate matching between the SA oscillation rate and RR can be so tight that some research protocols accept the SA rate as a proxy measurement for RR [2, 4]. Yet the SA rate and RR are not equal under all physiological conditions. For instance, during exertion or bradycardia, the SA rate is driven by non-respiratory factors, even in subjects with otherwise normal autonomic control systems [6, 7].

This physiology has major implications for comprehending why a particular HRV pattern would be diagnostically associated with a particular disease state or a healthy state. Consider the case of a patient exhibiting an atypical HRV pattern. This atypical HRV could be caused by any of the following: *1)* an atypical respiratory pattern driving an atypical SA pattern via a typical autonomic control system; *2)* an atypical driver (i.e., non-respiratory) causing an atypical SA pattern; or *3)* an atypical control system directly producing an atypical SA pattern. Interestingly, most prior reports in trauma patients ascribed distinctive HRV patterns to differences in autonomic tone, without detailed consideration of the underlying causes, such as respiratory or non-respiratory drivers [8-11].

The present study is intended to better understand the causes of HRV patterns in trauma patients, here focusing on neurologically intact, hemodynamically stable patients. We seek to answer the following questions: *First, under what conditions are the SA rate and the RR tightly matched? Second, are the findings consistent with reports of healthy laboratory subjects?* To address this, we explored a population of patients monitored during transport to the hospital after an episode of physical trauma. We examined how the relationship between SA rate and RR changed as a function of HR, RR, and their ratio (*HR/RR*).

II. Methods

A. Clinical Data Collection

Physiological data for this study was collected from 898 trauma patients during medical helicopter transport between August 2001 and April 2004 from the scene of injury to the level I unit at the Memorial Hermann Hospital in Houston, TX [8]. Additional attribute data were collected retrospectively via chart review. The time-series variables were measured by Propaq 206EL vital-sign monitors (Welch Allyn, Skaneateles Falls, NY), downloaded to an attached personal digital assistant, and ultimately stored in our database. Physiological data included the electrocardiogram (ECG; sampled at 182 Hz), a respiratory waveform (an impedance pneumograph, IP, measured through the ECG leads and sampled at 23 Hz), their corresponding monitor-computed HR and RR (recorded at 1-s intervals), and other

This work was supported by the U.S. Department of Defense Medical Research and Development Program (Grant No. D10_I_AR_J6_773) and by the Combat Casualty Care Research Area Directorate of the U.S. Army Medical Research and Materiel Command (USAMRMC), Fort Detrick, MD.

X. Chen was with the Department of Defense Biotechnology High Performance Computing Software Applications Institute (BHSAI), Telemedicine and Advanced Technology Research Center (TATRC), USAMRMC, Fort Detrick, MD 21702 USA.

A. T. Reisner is with the BHSAI, TATRC, USAMRMC, Fort Detrick, MD 21702 USA and with the Department of Emergency Medicine, Massachusetts General Hospital, Boston, MA 02114 USA (e-mail: areisner@partners.org).

L. Chen was with the BHSAI, TATRC, USAMRMC, Fort Detrick, MD 21702 USA.

S. Edla is with the BHSAI, TATRC, USAMRMC, Fort Detrick, MD 21702 USA (corresponding author; phone: 301-619-1977; fax: 301-619-1983; e-mail: sedla@bhsai.org).

J. Reifman is a Senior Research Scientist and Director of the BHSAI, TATRC, USAMRMC, Fort Detrick, MD 21702 USA (e-mail: jaques.reifman.civ@mail.mil).

standard vital-sign data. Patient attribute data included demographics, injury descriptions, pre-hospital interventions, and hospital treatments. Data collection and analysis was performed with the approval of both the local and the United States Army's human subjects Institutional Review boards (the latter at Fort Detrick, MD).

B. Study Population

We selected relatively healthy subjects for analysis according to the following attributes: no major hemorrhage that required the transfusion of red blood cells, no prehospital or hospital intubation, head abbreviated injury scale equal to 0, and Glasgow coma scale of 13 or higher.

In these subjects, we split time-synchronized ECG and IP waveforms into successive 2-min data segments and only analyzed those with reliable waveforms based on our previously developed quality index, which rated the waveforms as reliable if they were clean with rhythmic and consistent beats or breaths [12, 13]. Visual inspection to ensure that the ECG contained no ectopic beats resulted in the exclusion of a total of five 2-min data segments, all from the same subject. In total, 470 2-min recordings from 110 subjects (age, mean ± standard deviation): 39 ± 12 yr, age range: 18-76 yr, 86 men and 24 women, median of three data segments per subject) formed the study dataset.

C. Estimation of SA Rate, HR, and RR

For each 2-min ECG and IP waveform, we computed second-by-second HR and RR values using automated computer algorithms that have been previously reported and demonstrated to match human experts' estimation [12, 13].

We used the following method to construct the R-R interval (RRI) time series used to estimate the SA rate. First, we upsampled each ECG segment to 2000 Hz by cubic spline interpolation and detected R-wave time locations in the upsampled ECG using the method described in [13]. Second, we calculated RRIs as the difference between the time locations of successive R-waves, i.e., $RRI_i = R_{i+1} - R_i$ (i = 1, …, N-1; where N is the total number of R-waves), and located them at time location R_{i+1}. Third, we transformed the unevenly spaced RRI time series into an evenly spaced one with a sampling frequency of 23 Hz (the same as that of the IP waveforms) using cubic spline interpolation. Next, to count the SA cycles within the RRI waveform, we treated the RRI time series as a form of respiratory waveform and applied our previously developed RR estimation and reliability algorithms to compute the second-by-second SA rate and determine whether the waveform was of adequate reliability [12]. Finally, we averaged the reliable SA rate and corresponding HR and RR within the same time period for each 2-min recording and performed an analysis based on the mean SA rate, HR, and RR. Because the HR and RR were estimated from reliable ECG and IP waveforms, no further reliability filtering was implemented.

D. Determination of SA-RR Matching

Although the overall relationship between SA and respiration can be mathematically quantified by coherence and cross-approximate entropy [14, 15], the results may be difficult to interpret. For a simple and practical approach to determine whether or not each 2-min data segment showed SA-RR matching, we visually inspected the 2-min normalized RRI time series and IP waveform pairs by examining every non-overlapping 15-s data segment, and identified whether there was a consistent pattern of alteration between each SA oscillation and each respiratory oscillation. If at least 75% of consecutive 15-s RRI and IP waveform pairs exhibited alternating SA and RR oscillations, we considered the whole 2-min data segment to represent an SA-RR matching case. Otherwise, it was considered as not rate matched.

Visual determination of SA-RR matching was based on the judgment of a single investigator and objectively corroborated using automated algorithms to calculate the difference between the SA rate and RR (confirming that for matched segments, the difference between SA rate and RR was within ±5 cycles per minute [cpm]).

E. Data Analysis

To quantify the agreement between SA rate and RR, we calculated the Pearson's correlation coefficient (r_p) and the concordance correlation coefficient (r_c) between SA rate and RR. While the well-known r_p quantifies the linear relationship between two variables regardless of the slope and x-intercept of the regression line, r_c quantifies the linear relationship with respect to the identity line [16] and is thus a better metric to measure the degree to which two variables are equal to each other. Next, we computed the percentage of data segments that lack SA-RR matching within each HR, RR, and *HR/RR* range. The 95% confidence intervals (CIs) of the percentages were also calculated [17].

III. Results

In this dataset, r_p between the SA rate and RR was 0.43, and r_c was 0.39, reflecting a significant but moderate overall correlation. Of the 110 subjects under study, 43% of the subjects exhibited SA-RR matching for each of their 2-min data segments, 27% of the subjects lacked SA-RR matching for each of their 2-min data segments, and the remaining 30% of the subjects exhibited a mix of present and absent SA-RR matching in different 2-min data segments. For the data segments that exhibited matching via visual inspection, we found a high agreement between the automatically computed SA rate and RR (the difference between the SA rate and RR was within ±5 cpm for 93% of those segments).

Fig. 1 illustrates the SA-RR relationship using three selected pairs of sample ECG, RRI, and IP waveforms. A tight SA-RR matching with $2.4 \leq HR/RR < 4.8$ (*left*), lack of SA-RR matching with a higher (than RR) SA rate and $HR/RR \geq 4.8$ (*middle*), and lack of SA-RR matching with a lower (than RR) SA rate and $HR/RR < 2.4$ (*right)* were some of the typical patterns observed.

Fig. 2 shows the percentage (along with 95% CIs) of data segments that lacked SA-RR matching in different *HR/RR*, RR, and HR ranges. Fig. 2A shows that both low and high *HR/RR* values were associated with a high fraction of data segments that lacked SA-RR matching. When $HR/RR < 2.4$, 81% of the 2-min data segments lacked SA-RR matching;

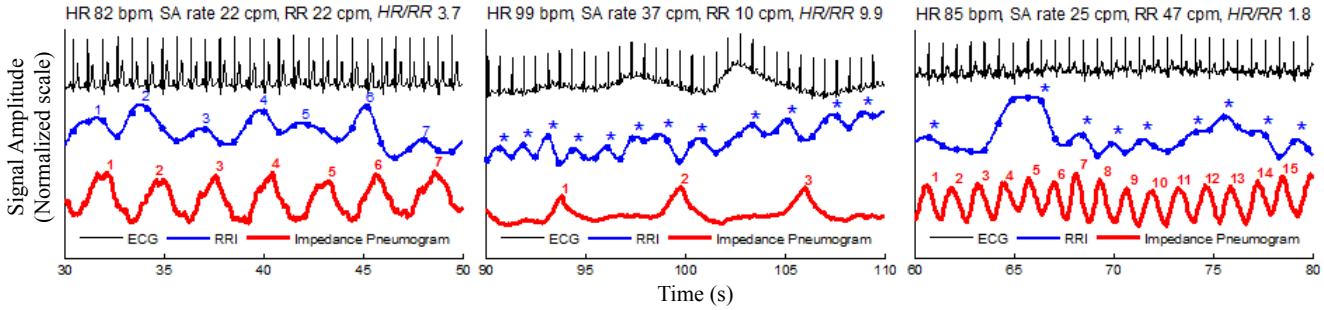

Figure 1. Examples of ECG, RRI, and impedance pneumogram waveforms. *Left*: Rate matching between SA and respiration. *Middle*: Absence of SA-RR matching (with tachycardia and bradypnea). *Right*: Absence of SA-RR matching (with HR almost double RR). Symbols above the respiratory and RRI waveforms (* and numerals, respectively) denote distinct oscillations that were identified by automated computer algorithms. ECG: electrocardiogram, HR: heart rate, RR: respiratory rate, RRI: R-R interval time series, SA: sinus arrhythmia.

when *HR/RR* ≥ 4.8, 86% of the 2-min data segments lacked SA-RR matching. We also found independent associations between rate matching and RR, as well as HR. Figs. 2B and 2C show that ≥ 57% of the 2-min data segments with RR ≥ 30 cpm, and 55% of the 2-min data segments with HR < 60 beats per minute (bpm), respectively, lacked SA-RR matching.

IV. Discussion

In this study, in a population of relatively healthy patients (i.e., no hemorrhage nor serious neurological injury) early after major trauma, we investigated when SA oscillation was predominantly driven by respiration and we proposed a simple metric that can determine when SA-RR matching is likely.

We found a lack of SA-RR matching when RR was elevated ≥ 28 cpm (Fig. 2), where the SA rate tended to be lower than the RR. This likely reflected the inability of the sinoatrial node to oscillate fast enough to keep up with rapid respiration, as reported in previous studies [18, 19] wherein the transfer function between vagal nerve impulses and the sinoatrial node rate exhibited the characteristics of a low pass filter with a cutoff frequency of ~0.5 Hz, or 30 cpm. Above this cut-off, the SA rate cannot keep up with RR. This was very close to our cut-off of 28 cpm suggesting comparable SA rate cut-offs in both uninjured trauma patients and healthy laboratory subjects.

In this dataset, there was an absence of SA-RR matching when HR was low, e.g., < 60 bpm. This is related to cardiac aliasing [7]. Cardiac aliasing is mathematically inevitable unless HR is equal to or greater than twice RR (i.e., *HR/RR* ≥ 2), because it requires at least two heart periods for each respiratory cycle to establish an oscillation (an oscillation requires, at minimum, one shorter interval that alternates with a second, longer interval).

When HR was elevated, e.g., HR > 100 bpm, the SA rate exceeded RR in approximately 50% the cases, whereas in the other 50% there was SA-RR matching. The association between tachycardia and reduced SA-RR matching was previously observed in athletes during exercise, who exhibited rapid SA rates (> RR) [6]. This phenomenon was attributed to the fact that the cardiovascular system that coupled respiration to HR had nonlinear components and that harmonics of RR could appear in the output HR time series [20]. Furthermore, in normal subjects, the cardiac vagal system served as strong, fast negative feedback, attenuating the harmonics in the HR time series. However, in young athletes during exercise, as well as in heart transplant patients, the vagal control was either minimal or absent, and a higher (than RR) SA rate was observed. It was concluded that elevated SA rate was thus an indicator of reduced vagal control of the heart.

In terms of anticipating whether or not rate matching would occur in our dataset, it was more effective to consider the ratio *HR/RR* than to look for the presence of tachycardia alone (Fig. 2). What we found in terms of *HR/RR* versus rate matching was wholly consistent with a prior report by Cysarz et al. [2], wherein an r_c of 0.64 was observed between SA rate and RR within a laboratory population (for a population with 3.0 < *HR/RR* < 8.7, approximately). For the comparable subset of our study population who had 3.0 < *HR/RR* < 8.7, we found a rather similar result with r_c = 0.60.

In contrast, the correlation between SA rate and RR was reported to be r_c = 0.95 (when 6 cpm < RR < 30 cpm) in [4]. For a comparable subset of our study population who had 6 cpm < RR < 30 cpm, we obtained an r_c = 0.27, which is far lower than the value reported in [4]. Does this mean our findings are inconsistent? Not necessarily. The study in [4] did not report the HR (unlike [2]); It is entirely possible, if not likely, that our population had a relative elevation in HR. Also, in [4] subjects were studied during supine rest in a laboratory, whereas we studied acute trauma patients during prehospital care. This underlies one of our major findings, that it is necessary to consider HR and RR simultaneously when trying to determine whether SA-RR matching is likely to occur in a typical population.

In general, the *HR/RR* metric provided a compact summary of all of our aforementioned findings: (a) when 2.4 ≤ *HR/RR* < 4.8, SA and respiration were typically rate matched; (b) when *HR/RR* was high (i.e., ≥ 4.8), there might be high HR indicating vagal withdrawal and the resultant elevated SA rate [20]; and (c) when *HR/RR* was low (i.e., <

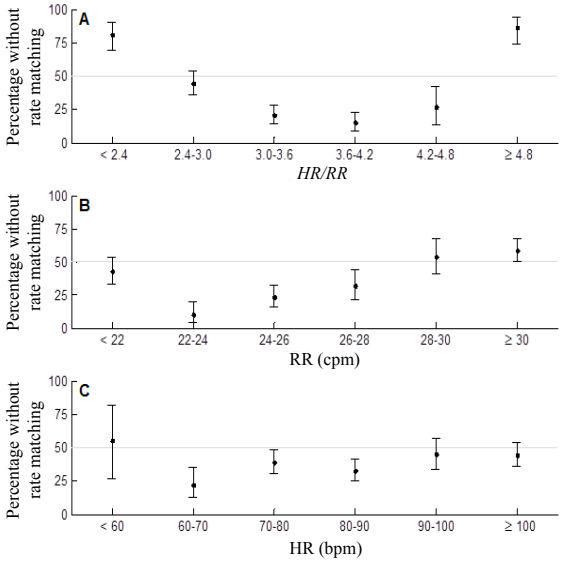

Figure 2. The percentage of data segments that lacked SA-RR matching for different *(A) HR/RR*, (*B*) RR, and (*C*) HR ranges. The vertical bars represent the 95% confidence intervals. The grey gridline indicates 50% of data segments. The largest percentage of data segments that lacked SA-RR matching was observed when *HR/RR* < 2.4 or *HR/RR* ≥ 4.8. bpm: beats per min, cpm: cycles per min, HR: heart rate, RR: respiratory rate, SA: sinus arrhythmia.

2.4), there were two phenomena that caused the absence of SA-RR matching. First, the RR might be so elevated that the sinoatrial node could not keep up with the rapid respiratory oscillations [18]. Second, cardiac aliasing would likely have occurred.

Our findings support the validity of laboratory-based investigation as a model for actual trauma patients, and confirm that respiration is frequently the predominant driver of SA in trauma patients without major injuries. A second implication relates to studies that investigate whether or not SA rate monitoring can serve as a suitable RR proxy [2, 4]. Our findings suggest that, in a population similar to these trauma patients, this methodology will work provided that HR is neither too fast nor too slow and there is no tachypnea. The *HR/RR* metric might have anticipated the findings in [4], wherein a very high correlation was reported between SA rate and RR at rest, as well as the findings in [2], wherein reduced correlation was seen in subjects during low levels of exercise. Finally, we expect that our findings may be informative to future studies into the determinants of HRV in trauma patients, by providing a better understanding of those trauma patients without serious injury.

DISCLAIMER

The opinions and assertions contained herein are the private views of the authors and are not to be construed as official or as reflecting the views of the U.S. Army or of the U.S. Department of Defense. This paper has been approved for public release with unlimited distribution.

REFERENCES

[1] T. Buchner, "HRV strongly depends on breathing. Are we questioning the right suspect?," in *Conf. Proc. IEEE Engineering in Medicine and Biology Society*, Boston, MA, 2011, pp. 7739-7742.

[2] D. Cysarz, R. Zerm, H. Bettermann, M. Fruhwirth, M. Moser, and M. Kroz, "Comparison of respiratory rates derived from heart rate variability, ECG amplitude, and nasal/oral airflow," *Ann. Biomed. Eng.,* vol. 36, pp. 2085-2094, 2008.

[3] J. A. Hirsch and B. Bishop, "Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate," *Am. J. Physiol. Heart Circ. Physiol.,* vol. 241, pp. H620-H629, 1981.

[4] A. Schafer and K. W. Kratky, "Estimation of breathing rate from respiratory sinus arrhythmia: comparison of various methods," *Ann. Biomed. Eng.,* vol. 36, pp. 476-485, 2008.

[5] J. F. Thayer, J. J. R. Sollers, E. Ruiz-Padial, and J. Vila, "Estimating respiratory frequency from autoregressive spectral analysis of heart period," *IEEE Eng. Med. Biol. Mag.,* vol. 21, pp. 41-45, 2002.

[6] L. Bernardi, F. Salvucci, R. Suardi, P. L. Solda, A. Calciati, S. Perlini, C. Falcone, and L. Ricciardi, "Evidence for an intrinsic mechanism regulating heart rate variability in the transplanted and the intact heart during submaximal dynamic exercise?," *Cardiovasc. Res.,* vol. 24, pp. 969-981, 1990.

[7] H. Witte, U. Zwiener, M. Rother, and S. Glaser, "Evidence of a previously undescribed form of respiratory sinus arrhythmia (RSA)--the physiological manifestation of "cardiac aliasing"," *Pflugers Arch.,* vol. 412, pp. 442-444, 1988.

[8] W. H. Cooke, J. Salinas, V. A. Convertino, D. A. Ludwig, D. Hinds, J. H. Duke, F. A. Moore, and J. B. Holcomb, "Heart rate variability and its association with mortality in preshospital trauma patients," *J. Trauma,* vol. 60, pp. 363-370, 2006.

[9] E. L. Grogan, J. A. Morris, P. R. Norris, D. J. France, A. Ozdas, R. A. Stiles, P. A. Harris, B. M. Dawant, and T. Speroff, "Reduced heart rate volatility: an early predictor of death in trauma patients," *Ann. Surg.,* vol. 240, pp. 547-554, 2004.

[10] K. G. Proctor, S. A. Atapattu, and R. C. Duncan, "Heart rate variability index in trauma patients," *J. Trauma,* vol. 63, pp. 33-43, 2007.

[11] R. J. Winchell and D. B. Hoyt, "Analysis of heart-rate variability: a noninvasive predictor of death and poor outcome in patients with severe head injury," *J. Trauma,* vol. 43, pp. 927-933, Dec 1997.

[12] L. Chen, T. McKenna, A. T. Reisner, and J. Reifman, "Algorithms to qualify respiratory data collected during the transport of trauma patients," *Physiol. Meas.,* vol. 27, pp. 797-816, 2006.

[13] C. Yu, Z. Liu, T. McKenna, A. T. Reisner, and J. Reifman, "A method for automatic identification of reliable heart rates calculated from ECG and PPG waveforms," *J. Am. Med. Inform. Assoc.,* vol. 13, pp. 309-320, 2006.

[14] K. J. Bar, A. Schuhmacher, S. Hofels, S. Schulz, A. Voss, V. K. Yeragani, W. Maier, and A. Zobel, "Reduced cardio-respiratory coupling after treatment with nortriptyline in contrast to S-citalopram," *J. Affect. Disord.,* vol. 127, pp. 266-273, Dec 2010.

[15] S. Berger, M. K. Boettger, M. Tancer, S. M. Guinjoan, V. K. Yeragani, and K. J. Bar, "Reduced cardio-respiratory coupling indicates suppression of vagal activity in healthy relatives of patients with schizophrenia," *Prog. Neuropsychopharmacol. Biol. Psychiatry,* vol. 34, pp. 406-411, Mar 17 2010.

[16] L. Lin, "A concordance correlation coefficient to evaluate reproducibility," *Biometrics,* vol. 45, pp. 255-268, 1989.

[17] T. D. Ross, "Accurate confidence intervals for binomial proportion and Poisson rate estimation," *Comput. Biol. Med.,* vol. 33, pp. 509-531, Nov 2003.

[18] R. D. Berger, J. P. Saul, and R. J. Cohen, "Transfer function analysis of autonomic regulation. I. Canine atrial rate response," *Am. J. Physiol. Heart Circ. Physiol.,* vol. 256, pp. H142-H152, 1989.

[19] J. P. Saul, R. D. Berger, M. H. Chen, and R. J. Cohen, "Transfer function analysis of autonomic regulation. II. Respiratory sinus arrhythmia," *Am. J. Physiol. Heart Circ. Physiol.,* vol. 256, pp. H153-H161, 1989.

[20] E. Toledo, I. Pinhas, D. Aravot, and S. Akselrod, "Very high frequency oscillations in the heart rate and blood pressure of heart transplant patients," *Med. Biol. Eng. Comput.,* vol. 41, pp. 432-438, 2003.