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Inconsistent relation of nonlinear heart rate variability indices to increasing vagal tone in healthy humans☆

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ABSTRACT

Background: Prior work has found that linear heart rate variability (HRV) indices do not accurately reflect cardiac vagal control, and nonlinear indices of HRV have been proposed as alternative tools that may better capture cardiac vagal effects. We used progressive low dose atropine to induce changes in cardiac vagal tone to test the hypotheses that nonlinear HRV indices accurately reflect cardiac vagal control, and that their changes in response to low dose atropine correlate with those in RR interval.

Methods: Changes in RR interval and HRV indices during intravenous injections of saline (control) and 6 cumulative doses of atropine (from 1.4 to 7.2 μg/kg) during controlled breathing at 15 breaths per minute were assessed in 14 young healthy individuals.

Results: As expected, low dose atropine increased average RR interval (vagotonic effect). There was no strong association between vagotonic changes in RR interval and the majority of nonlinear HRV indices, either within or among subjects.

Conclusions: These data suggest an inconsistent relationship between responses of nonlinear HRV indices and RR interval to changes in cardiac vagal tone. Therefore, nonlinear HRV indices may not be reliable indices of cardiac vagal control in healthy humans.

1. Introduction

It is generally accepted that cardiac vagal modulation is among the primary mediators of fluctuations across heart beats (Task Force, 1996). Thus, heart rate variability (HRV) has been proposed to assess the autonomic influence on cardiac sinus rhythm (Task Force, 1996), and has been explored as a predictor of outcomes in cardiovascular diseases (Kleiger et al., 1987). However, in the last two decades, it has become evident that the magnitude of variability, assessed via traditional methods, may not directly relate to cardiac vagal modulation. For example, while respiratory sinus arrhythmia (RSA) seems to represent cardiac vagal control to some degree, sympathetic outflow may also affect the magnitude of RSA (Taylor et al., 2001). Similarly, time domain estimates of global variability do not always track vagal tone (Picard et al., 2009). As a result, there have been attempts to employ alternative analyses to extract information from HRV that may more explicitly assess cardiac vagal modulation.

Among these alternative analyses are nonlinear approaches to describe patterns in HRV. For example, the Poincaré plot, a geometric plot of the current versus successive RR intervals (RRi), has been suggested to encompass a short-term correlation that reflects vagal modulation (Kamen et al., 1996). This has been extended to symbolic analysis of heart rate, which transforms a time series of R-R intervals (RRi) into discrete 3-beat patterns based on current and preceding beats (Guzzetti et al., 2005; Porto et al., 2016). It has been posited that sets of three beats demonstrating a pattern of two unequal changes represents vagal modulation. Somewhat similarly, deceleration capacity derives from a single increase in RRi from one beat to the next in a phase rectified, signal averaged time-series. This rapid 'deceleration' has been suggested to reflect vagal modulation (Bauer et al., 2006). An alternative

Abbreviations: HRV, Heart rate variability; RSA, respiratory sinus arrhythmia; HR, Heart rate; RRi, RR intervals; SDNN, the standard deviation of all RRi; RMSSD, square root of the mean of the sum of the squares of differences between adjacent normal-to-normal intervals; SD1, the perpendicular dispersion to the line of identity; SD2, the length of the plot along the line of identity; 0 V%, patterns with no variation; 1 V%, patterns with one variation; 2LV%, patterns with two like variations; 2UV%, pattern with two unlike variations; DC, Deceleration capacity; AC, Acceleration capacity; PIP, The percentage of inflection points; IALS, The inverse of the average length; PSS, The percentage of short segments; PAS, The percentage of RRi in alternation segments

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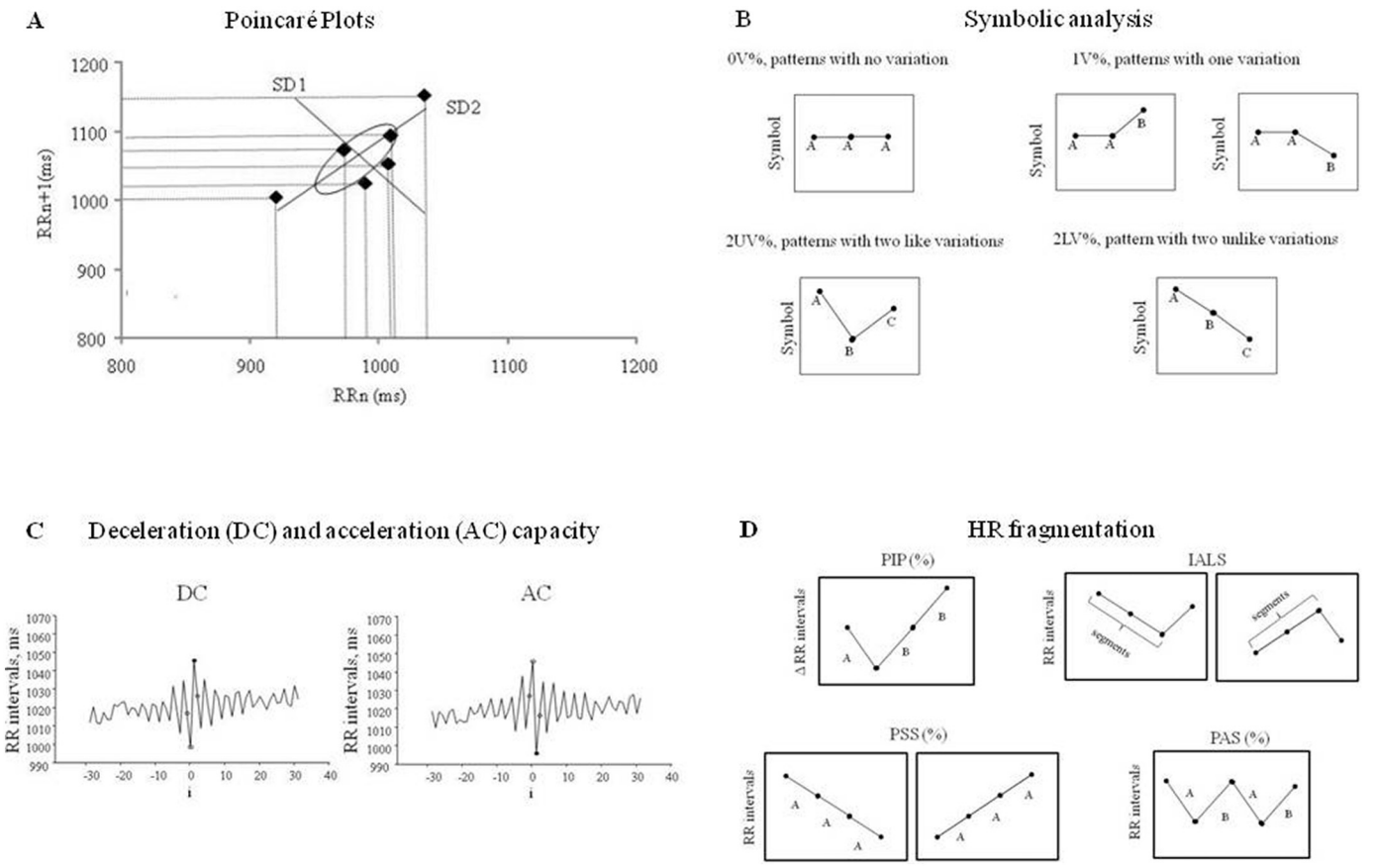

Fig. 1. Schematic variations for Poincaré Plots (Panel A), symbolic analysis (Panel B), Deceleration (DC) and acceleration (AC) capacity (Panel C) and HR fragmentation (Panel D).

approach is heart rate fragmentation that has been proposed to characterize short-term uncorrelated beat-to-beat patterns and to derive four fragmentation indices to capture cardiac vagal modulation (Costa et al., 2017). Although all of these indices have been claimed to assess purely vagal activity, this has not been explicitly tested.

Low doses of atropine have a parasympathomimetic effect and increase the average RRi in a dose-dependent matter (Averill and Lamb, 1959). Vagotonic doses of atropine also result in changes in RSA and time domain measures of HRV, which, however, may or may not correlate with the changes in RRi (Picard et al., 2009). If nonlinear HRV indices indeed reflect vagal modulation accurately, their changes should correlate best with changes in RRi under progressive low doses of atropine. Therefore, we set out to test the hypothesis that changes in nonlinear HRV indices correlate with the physiological effect of progressive low dose atropine on RRi and on traditional time domain variabilities in healthy individuals.

2. Methods

2.1. Study population

Fourteen young healthy males ($N = 8$) and females ($N = 6$) participated in this study. Subjects were eligible if they were nonsmokers, without history of cardiovascular disease, and were taking no medications. Subjects were not engaged in regular physical activity. They averaged 26 ± 1 yrs. in age and 20.8 ± 2.2 kg/m^2 in BMI. Average resting heart rate (HR) was 63 ± 3 bpm and resting blood pressures were 114 ± 5 mmHg systolic and 66 ± 3 mmHg diastolic. All volunteers were instructed to refrain from performing any vigorous activity and consuming alcohol or caffeine 24 h prior to testing. This research was approved by the Institutional Review Board at Spaulding Rehabilitation Hospital and all subjects gave written informed consent to participate.

2.2. Experimental design

All testing was performed in the morning with subject in an overnight fast and in the supine position. After insertion of an antecubital venous catheter for atropine administration a full instrumentation by electrocardiogram, oscillometric blood pressure, respiratory bellows were measurements. Atropine doses were 0 μg/kg (saline control), followed by 6 progressive doses (cumulative: 1.4, 2.2, 3.2, 4.4, 5.8, 7.2 μg/kg). Atropine administration was stopped if the subject reported symptoms of systemic cholinergic blockade (e.g., dry mouth, sensitivity to light, and/or increase in heart rate by > 10 beats/min). The electrocardiogram was acquired for 5 min and used the last 3 min for analysis at each dose of atropine, with breathing paced at 0.25 Hz (15 breaths/min) in response to an auditory signal. Throughout the study, electrocardiogram lead II was digitized at a rate of 1000 Hz and stored for offline analysis (Power Lab, ADInstruments).

2.3. Data analysis

All data analysis was performed using custom written software in MATLAB (version R2010a). R peaks were identified to derive beat-by-beat RRi time series for each subject. The standard deviation of RRi (SDNN) and the square root of the mean sum of squares of successive differences (RMSSD) were calculated as traditional time-domain indices of HRV. RSA was calculated via power spectral analysis based on the Welch algorithm as described previously (Taylor et al., 2001).