Heart rate variability measurements

A raw single-lead digital ECG signal (sampling rate 200Hz; amplitude resolution 4.88μV) was analyzed in the Tereshchenko laboratory at the Oregon Health & Science University. A custom MATLAB (The MathWorks, Inc, Natick, MA, USA) software application was developed (NMR, EAPA, YLP, MMK; provided at https://github.com/Tereshchenkolab/HRV) to automatically detect QRS complexes and select a single 3-minute normal sinus rhythm epoch for each hour of recording. The algorithm automatically eliminated epochs with premature R_2 beats if the R_1R_2 interval was shorter than the preceding R_0R_1 interval by 15% or greater. The algorithm similarly eliminated epochs with a sudden pause, if subsequent the R_1R_2 interval was longer than the preceding R_0R_1 interval by 15% or greater, to remove epochs with blocked premature atrial or His extrasystoles, or intermittent sinoatrial or AV block. Traditionally, in Holter ECG analysis, the premature atrial beat was defined by a coupling interval of less than 80% of the mean RR interval.[1] We applied a more stringent threshold after manually reviewing our ECG data with the thresholds ranging from 2-20%. A sliding 3-minute window approach was used to scan the entirety of the data: when a premature beat (or sudden pause) was detected, the premature beat and subsequent compensatory pause were skipped, and a new 3-minute window search started thereafter again. If the algorithm did not find a continuous 3-minute epoch of sinus rhythm in an entire hour, the software would change the R-peak detection algorithm[2] and repeated all described above steps. The first R-peak detection algorithm employed was a Pan-Tompkins,[3] followed by principle component analysis,[4] and then parabolic fitting.[5] Because the magnitude of R and S peaks varied within and between patients, the dominant peak of the QRS complex varied during long-term ECG monitoring. We paid special attention to ensure consistent signs of the dominant QRS peak for the entire 3-minute epoch. The greatest average

Manhattan distance from baseline to the highest positive (R) peak and highest negative (S) peak was calculated to identify the best dominant peak for each 3-minute epoch. The accuracy of consistent dominant (R or S) peaks detection, and accuracy of the selection of consecutive normal sinus beat were validated on a data subset by the investigator (NMR), with the aid of a graphical display (Figure 2).

HRV was measured according to the Standards.[6, 7] Developed (by MMK) MATLAB (the MathWorks, Inc, Natick, MA, USA) software code is provided at https://github.com/Tereshchenkolab/HRV.

Time-domain heart rate variability measures

Heart rate and the root mean square of the successive normal sinus to normal sinus (NN) intervals differences (rMSSD) were calculated for each 3-minute epoch selected per hour.

Frequency-domain heart rate variability measures

The low frequency (LF; 0.04-0.15 Hz) power, high frequency (HF; 0.15-0.4 Hz) power, and LF/HF ratio of powers were calculated for each 3-minute epoch.

Nonlinear heart rate variability measures

Quantitative analysis of the Poincaré plot was performed.[7] The Poincaré plot was derived from every 3-minute NN data epoch by plotting the values NN_{n+1} against the values of NN_n. SD_1 was calculated as the standard deviation (SD) of the cloud of points in the direction perpendicular to the line-of-identity. SD_2 was calculated as the SD of the cloud of points in the direction of the line-of-identity. SD_1/SD_2 ratio was called SD_{12}.

Entropy

To quantify the entropy rate on a short-length NN series, we elected to measure sample entropy[7] and Renyi entropy for each 3-minute epoch. Renyi entropy was calculated as described

by Cornforth *et al*.[8] We used an α value equal to 4 because of previous data suggesting that positive α (1-5) provides the best discrimination of cardiac autonomic neuropathy, and based on the sampling rate of our data.[9]

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