Supplementary Materials: Measuring Electromechanical Coupling in Patients with Coronary Artery Disease and Healthy Subjects

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In order to better understand the availability of our proposed bivariate cardiac electromechanical coupling analysis, we also performed univariate HRV analysis based on the same data set. Analysis methods are described below. Subjects, data acquisition and construction of HRV series (RR series) can be found in the main text.

1. Methods for analysing HRV Series

1.1. Time-domain Measurement

Standard deviation of all normal to normal intervals (SDNN) of the HRV series was applied as the time-domain measurement [1]. SDNN is defined by:

$$\mathrm{SDNN} = \sqrt{\frac{\sum_{i=1}^{N}\left(RR_i - RR_{mean}\right)^2}{N}},$$

where N is number of RR intervals in 5 min, RR_i is value of the i-th RR interval and RR_{mean} is the mean value of all RR intervals in 5 min.

1.2. Frequency-domain Measurements

Low-frequency (LF, 0.04~0.15 Hz) and high-frequency (HF, 0.15~0.4 Hz) as the frequency-domain measurements [1]. Prior to frequency-domain analyses, the HRV series were evenly resampled with a sampling frequency of 4 Hz by spline interpolation, their corresponding power spectral density was finally performed by the Burg's method with 16th order [2].

1.3. Nonlinear Measurements

We calculated the sample entropy (SampEn), fuzzy entropy (FuzzyEn) and refined fuzzy entropy (rFuzzyEn) of HRV in healthy subjects and CAD patients as the nonlinear measurements (the HRV series without evenly resampling were used). They are defined as follows:

For a length-N series $\left\{x_i, i = 1,2,\cdots,N\right\}$, form vector $\mathbf{X}_i^{(m)}$ as $\mathbf{X}_i^{(m)} = \left[x_i, x_{i+1}, \cdots, x_{i+m-1}\right]$ ($i = 1,2,\cdots,N-m$). Define the distance between two vectors $\mathbf{X}_i^{(m)}$ and $\mathbf{X}_j^{(m)}$ by:

$$d_{ij}^{(m)} = \max\left(\left|x_{i+k} - x_{j+k}\right|\right)\Big|_{k=0}^{m-1},$$

where $i, j = 1,2,\cdots,N-m$, m is embedding dimension. For each $\mathbf{X}_i^{(m)}$, define the average number of $\mathbf{X}_j^{(m)}$ ($j = 1,2,\cdots,N-m \cap j \neq i$) which is similar to $\mathbf{X}_i^{(m)}$ by:

$$B_i^{(m)}\left(r\right) = \frac{\sum_{j=1, j\neq i}^{N-m} A\left(y\right)}{N-m-1},$$

where r is the threshold parameter, $A\left(y\right)$ indicates the membership function. Then, compute the mean of $B_i^{(m)}\left(r\right)$ by:

$$B^{(m)}\left(r\right) = \frac{\sum_{i=1}^{N-m} B_i^{(m)}\left(r\right)}{N-m}.$$

Similarly, define $B_i^{(m+1)}(r)$ as the average number of $\mathbf{X}_j^{(m+1)}$ which is similar to $\mathbf{X}_i^{(m+1)}$, and compute its mean $B^{(m+1)}(r)$, accordingly. Finally, the entropy can be estimated by:

$$En(m,r,N) = -\ln\frac{B^{(m+1)}(r)}{B^{(m)}(r)}.$$

The SampEn is formed when $A(y)$ is set as Heaviside function $\Theta\left(r - d_{ij}^{(m)}\right)$ [3], FuzzyEn is formed when $A(y)$ is set as Gaussian function $A(d,r) = e^{-\ln(2)(d/r)^2}$ [4,5] and rFuzzyEn when $A(y)$ is piecewise fuzzy membership function $A(d,r) = \begin{cases} 1, & 0 \le d < r \\ e^{-\ln(2)\left(\frac{d-r}{r}\right)^2}, & d \ge r \end{cases}$ [6]. The r value for three entropy measures was set at 0.2 × *sd* (standard deviation of the under-analysed series), the embedding dimension *m* was set at 2, here.

1.4. Statistical Analysis

HRV measurements were compared between the two groups by nonparametric Mann-Whitney *U* test. Statistical significance was accepted at $p < 0.05$. All statistical analyses were performed using SPSS (Version 20, IBM, USA).

2. HRV Analysis Results

Results are shown in Table S1. All results (including both linear and nonlinear measurements) demonstrate no significant difference between healthy subjects and CAD patients. In one of our previous publications [6], we have compared those HRV measurements between healthy subjects and CAD patients based on a subset of the dataset used in this study. By applying the complete data set, we obtained almost the same results as previously reported—none of the HRV measurements show statistically significant differences. The results, however, differ from previous findings [7–9]. Carney *et al*. [10] have reported that HRV results in CAD patients can be greatly influenced by certain psychological conditions, such as the major depression, the above difference may be partly because that we did not take those psychological conditions of the participants into consideration. Study population and physiological conditions of the participants during data acquisition might be other factors that account for this discrepancy. In view of the results in our main text, a combination of both univariate and bivariate methods may potentially be better for classifying CAD patients from healthy volunteers.

Table S1. HRV analysis results in terms of time-domain, frequency-domain, and nonlinear measurements.

Measurements	Healthy subjects	CAD patients	*p*
SDNN (ms)	26.86 (19.57 37.10)	22.93 (16.68 30.61)	0.11
LF (ms^2)	85.27 (50.11 199.78)	62.20 (20.72 143.58)	0.10
HF (ms^2)	102.60 (55.88 162.11)	91.50 (41.16 153.25)	0.63
SampEn	1.59 (1.50 1.81)	1.69 (1.54 1.81)	0.36
FuzzyEn	1.30 (1.13 1.38)	1.34 (1.23 1.44)	0.11
rFuzzyEn	0.96 (0.79 1.05)	0.99 (0.93 1.09)	0.10

Abbreviations: SDNN: standard deviation; LF: power of low-frequency band; HF: power of high-frequency band; SampEn: sample entropy; FuzzyEn: fuzzy entropy; rFuzzyEn: refined fuzzy entropy. Data are expressed as median (25% 75%).

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