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Heart rate variability parameters and ventricular arrhythmia correlate with pulmonary arterial pressure in adult patients with idiopathic pulmonary arterial hypertension

Hung-Tao Yi, MD [a,b,1], Yu-Cheng Hsieh, MD, PhD [a,b,e,1], Tsu-Juey Wu, MD, PhD [a,b], Jin-Long Huang, MD, PhD [a,b], Wei-Wen Lin, MD, PhD [a,d], Kae-Woei Liang, MD, PhD [a,b], Chieh-Shou Su, MD [a,b], Wan-Jane Tsai, MS [a], Kuo-Yang Wang, MD [a,c,*]

[a] Cardiovascular Center, Taichung Veterans General Hospital, Taichung, Taiwan
[b] Institute of Clinical Medicine and Cardiovascular Research Institute, Department of Medicine, National Yang-Ming University, Taipei, Taiwan
[c] Division of Cardiology, Cardiovascular Research Group, Institute of Medicine, Chung-Shan Medical University Hospital, Taichung, Taiwan
[d] Department of Life Science, Tunghai University, Taichung, Taiwan
[e] Department of Financial and Computational Mathematics, Providence University, Taichung, Taiwan

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ABSTRACT

Objective: This aim of this study was to correlate heart rate variability (HRV) parameters to pulmonary arterial pressure (PAP) in patients with purely idiopathic pulmonary arterial hypertension (IPAH).
Background: HRV is decreased in patients with PAH. Whether HRV indices can be used to assess PAP in IPAH patients remains unclear.
Methods: HRV parameters obtained by 24-h ECG were evaluated in 26 IPAH patients and 51 controls.
Results: Time-domain HRV parameters (SDNN, $p < 0.0001$; SDANN, $p < 0.0001$; RMSSD, $p = 0.006$) were lower in IPAH patients. Frequency-domain indices (high-frequency power, HFP, $p = 0.001$; low-frequency power, LFP, $p = 0.003$; total power, TP, $p = 0.001$) were also decreased in IPAH patients. In IPAH patients, RMSSD ($p = 0.001$), HFP ($p = 0.015$), and LFP ($p = 0.027$) were significantly correlated with PAP. IPAH patients had longer QTc intervals ($p < 0.0001$) and more premature ventricular contractions ($p < 0.0001$) than controls.
Conclusions: IPAH is associated with autonomic dysfunction. RMSSD, HFP, and LFP may be used as a supplemental tool to assess PAP in IPAH patients. IPAH patients with autonomic dysfunction are at high risk for ventricular arrhythmia.

Introduction

Idiopathic pulmonary arterial hypertension (IPAH) is a progressive disorder of the pulmonary vasculature, characterized by elevated pulmonary arterial pressure (PAP) and vascular resistance, leading to right ventricular (RV) failure.[1] There are ~15,000 deaths annually in the USA alone from this disease, and the median survival is only 5–6 years.[2] Despite the progress achieved during the last two decades with the introduction of targeted medical therapies, the prognosis for IPAH patients remains poor.

Heart rate variability (HRV) describes the oscillation in the intervals between consecutive heart beats.[3] The variation in HR is modulated by autonomic nervous system (ANS) that incorporates both sympathetic and parasympathetic activity.[3] Two major methods, including "time domain" and "frequency domain" analyses, have been developed to quantify the variation in HR. Time domain measures of HRV are assessed with calculations based on statistical operations on R–R intervals. Commonly used measures include the standard deviation (SD) of all normal-to-normal intervals (SDNN), the SD of mean values for all normal-to-normal

Abbreviations: 6MWT, 6-minute walking test; ANS, autonomic nervous system; HF, high frequency; HRV, heart rate variability; IPAH, idiopathic pulmonary arterial hypertension; LF, low frequency; LV, left ventricle; PAP, pulmonary arterial pressure; PAC, premature atrial contraction; PVC, premature ventricular contraction; QTcd, corrected QT interval dispersion; RAP, right atrial pressure; RMSSD, square root of the mean square differences of successive RR intervals; RV, right ventricle; SDANN, standard deviation of mean values for all normal-to-normal intervals over 5 min; SDNN, standard deviation of all normal-to-normal intervals; TP, total power; VLF, very low frequency.

* Corresponding author. Cardiovascular Center, Taichung Veterans General Hospital, No. 1650, Sec. 4, Taiwan Boulevard, Taichung 40705, Taiwan, ROC. Tel.: +886 4 2359 2525x3121; fax: +886 4 2374 1312.
E-mail address: wky830@gmail.com (K.-Y. Wang).

[1] The authors contributed equally to this work.

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intervals over 5 min (SDANN), and the square root of the mean square differences of successive RR intervals (RMSSD). Frequency domain measures use spectral analysis of a sequence of R–R intervals and provide information on how power (variance) is distributed as a function of frequency. Frequency-domain analyses yield up to 4 peaks in ultra low frequency (ULF: <0.003 Hz), very low frequency (VLF: 0.003–0.04 Hz), low frequency (LF: 0.04–0.15 Hz), and high frequency (HF: 0.15–0.4 Hz) ranges.[3]

The prognostic significance of HRV has been widely investigated in patients with various heart diseases.[4–8] ANS dysfunction presenting with decreased values of HRV parameters is associated with a poor prognosis and increased mortality in patients with ischemic and non-ischemic left ventricular (LV) dysfunction.[4–8] In patients with IPAH, long-standing RV pressure-overload leads to RV hypertrophy and subsequently RV failure.[9,10] Whether IPAH patients with predominant RV dysfunction have ANS impairment similar to that of patients with LV dysfunction remains unclear. Folino et al previously reported lower values of HRV parameters in 9 adult IPAH patients compared to the control group.[11] Lammers et al also showed that HRV predicted the outcome in 47 children with severe PAH of whom only 21 had IPAH.[12] In this study of a pure IPAH population, our aim was to investigate the role of HRV parameters in assessing PAP in patients with IPAH. Sudden death has been reported to account for 17–28% of mortality in patients with PAH. Previous studies also showed that the heart rate-corrected QT interval (QTc) and QTc dispersion (QTcd) are prolonged and associated with ventricular arrhythmia-related sudden death in a variety of structural heart diseases.[13–17] In patients with PAH (not only IPAH), Zhang et al found that QTc and QTcd were significantly prolonged, but no ventricular arrhythmia data were reported.[18] With the aid of 24-h ECG monitoring, we were able to explore the relationship between QTc/QTcd and ventricular arrhythmia in this IPAH patient group.

Methods

Patient selection

The study was approved by the Ethics Committee of Taichung Veterans General Hospital. We enrolled 26 patients (17 females and 9 males), in whom IPAH was diagnosed according to the ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension.[19] Fifty-one healthy subjects (34 females and 17 males) served as the control group. The control patients were free of obstructive sleep apnea syndrome, and they were not taking beta-blocker or angiotensin-converting enzyme inhibitor as part of their medication. The IPAH and control patients were all in sinus rhythm. All subjects underwent physical examination, chest X-ray, 12-lead ECG, 24-h ambulatory ECG monitors, and echocardiography. IPAH patients underwent additional examinations, including pulmonary function test, ventilation/perfusion lung scan, immunological profile, serum NT-pro B-type natriuretic peptide (BNP) level test, and right heart cardiac catheterization to confirm the diagnosis of IPAH. Clinical functional status was evaluated by a 6-minute walking test (6MWT) and the New York Heart Association (NYHA) functional classification for pulmonary hypertension.[20]

Twenty-four-hour ECG data were recorded from 11:00 AM to 11:00 AM of the next day by a DigiTrak XT Holter Recorder (Philips). Five unipolar electrodes were connected to the chest wall of patients to construct three pairs of bipolar leads (V1, V5, and aVF leads). The V1 lead recorded ECG with the electrodes located at the xiphoid process and sternal manubrium; the V5 lead recorded ECG between the left 5th intercostal space at the mid-clavicular line and manubrium sternum; and the aVF lead recorded ECG between the left and right 5th intercostal spaces at the mid-clavicular line. The ECG data were analyzed offline by Philips Zymed Holter 2010 Plus software.

Time-domain analysis

Time-domain analysis of HRV was accessed after collection of normal and aberrant complexes was completed, and all adjacent intervals between normal beats were analyzed. The time domain indices of HRV include: the standard deviation (SD) of all normal-to-normal intervals (SDNN), the SD of mean values for all normal-to-normal intervals over 5 min (SDANN), and the square root of the mean square differences of successive RR intervals (RMSSD). These HRV parameters have been shown to indicate the relationship between the ANS and cardiovascular mortality.[3,21]

Frequency-domain analysis

Fast Fourier transformation was used for the spectral analysis algorithm. The ECG data were analyzed in 10-min intervals throughout the recording. The results collected from each 10-min interval were averaged to form a composite spectrum. The range of 0–0.5 Hz was represented by 1000 harmonics. The data were expressed in non-linear scale (ms^2). Frequency-domain parameters included: total power (TP: 0–0.4 Hz), ULF (<0.003 Hz), VLF (0.003–0.04 Hz), LF (0.04–0.15 Hz) and HF (0.15–0.4 Hz). LF and HF were also presented by LF/HF ratio.[3,21]

QT interval and ventricular arrhythmia evaluation

The mean QT interval was calculated from the mean value of the consecutive cycles of each lead, and the QT interval dispersion was defined as the difference between the maximal and minimal QT values. Bazett's formula ($QTc = QT/\sqrt{RR}$) was used to obtain heart rate-corrected values of QT intervals (QTc) and their dispersions (QTcd). Ventricular arrhythmias were defined as the absolute number of premature ventricular contractions (PVC) detected within the recording time window.

Statistical analysis

All continuous values are expressed as mean ± SD. Differences between groups were examined for statistical significance by Mann–Whitney *U* test. Correlation between values was analyzed by linear regression. A p value of <0.05 was considered statistically significant.

Results

Baseline characteristics of IPAH patients

A total of 26 IPAH patients were enrolled in this study, and their baseline characteristics are shown in Table 1. The mean age of these patients was 45.4 ± 14.9 years with female predominant (65.4%). The mean PAP was 56.4 ± 15.3 mm Hg and most (73.1%) of these patients were classified as having NYHA class III status. The mean cardiac index was 2.0 ± 0.8 $l/min/m^2$ with a mean PCWP of 12.1 ± 6.9 mm Hg, suggesting that these patients were free of left ventricular dysfunction. Phosphodiesterase-5 inhibitor (sildenafil citrate) was prescribed for 65.4% of them, while endothelin receptor antagonist was given to 61.5% of them. A two-drug combination was given to 42.3% of the patients, while 23.1% of them were treated with a three-drug combination.