Heart Rhythm Complexity and PH

Subjects: Health Care Sciences & Services

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Pulmonary hypertension (PH) is a progressive, complex, and fatal disease. It involves heterogenous etiologies and different mechanisms, and eventually leads to right heart failure. The mortality of PH patients is high even after contemporary treatment. A non-invasive and convenient tool can measure PH risk by assessing heart rate variability (HRV), namely, heart rhythm complexity analysis.

Keywords: pulmonary hypertension ; heart rate variability ; non-linear analysis ; detrended fluctuation analysis ; multiscale entropy

1. Overview

Pulmonary hypertension (PH) is a fatal disease—even with state-of-the-art medical treatment. Non-invasive clinical tools for risk stratification are still lacking. The aim of this study was to investigate the clinical utility of heart rhythm complexity in risk stratification for PH patients. We prospectively enrolled 54 PH patients, including 20 high-risk patients (group A; defined as WHO functional class IV or class III with severely compromised hemodynamics), and 34 low-risk patients (group B). Both linear and non-linear heart rate variability (HRV) variables, including detrended fluctuation analysis (DFA) and multiscale entropy (MSE), were analyzed. In linear and non-linear HRV analysis, low frequency and high frequency ratio, DFAα1, MSE slope 5, scale 5, and area 6–20 were significantly lower in group A. Among all HRV variables, MSE scale 5 (AUC: 0.758) had the best predictive power to discriminate the two groups. In multivariable analysis, MSE scale 5 (p = 0.010) was the only significantly predictor of severe PH in all HRV variables. In conclusion, the patients with severe PH had worse heart rhythm complexity. MSE parameters, especially scale 5, can help to identify high-risk PH patients.

2. Pulmonary Hypertension

Pulmonary hypertension (PH) is a progressive, complex, and fatal disease. It involves heterogenous etiologies and different mechanisms [1], and eventually leads to right heart failure. The mortality of PH patients is high even after contemporary treatment [2]; however, timely and intensive management can improve outcomes even in high-risk patients. In addition, the dynamic adjustment of PH medications, based on disease status during follow-up, also plays an important role in PH management [3][4][5]. Therefore, a useful tool for PH risk stratification is urgently needed to guide PH treatment. Several prognostic factors of PH have been verified, including sex, exercise tolerance, right heart hemodynamics, and functional performance [6][7][8], and they have been applied in different prediction models.

In 2015, the European Society of Cardiology (ESC)/European Respiratory Society (ERS) PH guidelines first proposed a dynamic PH risk assessment tool, including a combination of imaging, biologic, hemodynamic, performance status, and clinical conditions [1]. This tool has shown good survival prediction between different risk groups [9][10]; however, it requires right heart hemodynamic measurements, which are invasive and difficult to apply for continuous monitoring of PH severity in clinical practice. Therefore, in this study, we propose a non-invasive and convenient tool for PH risk assessment derived from heart rate variability (HRV), namely, heart rhythm complexity analysis.

Heart rhythm complexity analyzes the complexity of changes in heart rate using non-linear methods, and it has been shown to have better predictive value for the diagnosis of PH and heart failure outcomes [11][12][13] than traditional HRV linear analysis [14]. In our previous study, we found that heart rhythm complexity was decreased in PH patients, and that it was useful to differentiate PH patients from normal populations [13]. However, whether heart rhythm complexity is useful in the risk stratification of PH patients is unknown. Therefore, we designed this study to investigate the clinical application of heart rhythm complexity in the risk stratification of PH patients.

3. Discussion

The main finding of this study was that heart rhythm complexity was significantly depressed in high-risk PH patients. In addition, adding heart rhythm complexity predictors to traditional linear HRV parameters improved the power to predict high-risk PH patients. This is the first study to demonstrate an association between heart rhythm complexity and severity of PH, and the better performance of heart rhythm complexity in identifying high-risk PH patients than traditional HRV parameters.

PH is a critical disease, which needs an early diagnosis and timely management. Patients classified as being at high risk according to the 2015 ESC/ERS PH guidelines have a worse prognosis compared to patients at low risk. Sitbon et al. demonstrated that poor functional status was associated with poor outcomes. In their study, PH patients in WHO functional class IV and those in class III with severely compromised hemodynamics had the worst outcomes [15]. Previous studies have demonstrated that early interventions including both pharmacological and multidisciplinary team care can improve the outcomes of PH patients, even those with severe disease and poor functional status [5]. Therefore, identifying high-risk patients is essential for the management of PH. Several survival prediction models have been proposed for PH patients; however, they are complex and difficult to use [16]. Currently, the 2015 ESC/ERS PH guidelines advocate assessing the risk of PH by using a combination of several different tools, and this method is widely used in daily practice [1]. However, risk assessment requires invasive right heart catheterization, which is difficult to apply in frequent monitoring during follow-up. Therefore, there is still a strong unmet need for an easy-to-use tool to allow for both timely and continuous monitoring of disease status to improve the clinical care of PH patients.

HRV is a useful non-invasive tool, which has been studied in many diseases, including coronary artery disease, heart failure, and even pulmonary hypertension [17][18][19]. It has been correlated with autonomic dysfunction and used as an outcome predictor. Porte et al. demonstrated that heart rate complexity parameters decreased due to sympathetic activation during postural change [20]. Another study showed that sympathetic activation during senescence was associated with impaired heart rate complexity [21]. These evidences supported that the usefulness of heart rate complexity in monitoring sympathovagal balance. Pulmonary hypertension is characterized by increased pulmonary artery pressure leading to right ventricular failure [22]. The serum norepinephrine increased in patients with PAH similar to those with congestive heart failure as the indicator of cardiac sympathetic activation [23]. Furthermore, sympathetic activation has also been correlated with the severity of PH [24][25]. Several studies also showing that measuring autonomic system regulation using HRV could be a predictor of disease severity and long-term outcomes in PH [26][27][28][29]. Since that, overactivation of sympathetic systems is likely to be one of the major reasons explaining the worse HRV and complexity in severe PH patients. Bienias et al. demonstrated that patients with arterial or chronic thromboembolic PH had significantly impaired heart rate turbulence, a linear HRV parameter [30]. Recently, Peng et al. proposed the heart rhythm complexity derived from two non-linear parameters of HRV, DFA, and MSE, to evaluate complexity change in the biological systems [31][32][33]. Heart rhythm complexity was shown to have better efficacy and predictive power for various diseases than traditional HRV [14][34].

Heart rhythm complexity measures the complexity of changes in the R–R interval, which contains detailed information derived from heart rate dynamics. Once a biological system has become diseased, the complexity breaks down, and non-linear HRV analysis, can detect subtle changes at an early stage [35]. In a retrospective study, abnormal DFAα1 in asymptomatic heart failure patients was associated with the onset of heart failure years in advance of the first clinical event [36][37]. Tsai et al. recently demonstrated that heart rhythm complexity had a better prognostic value for cardiovascular events in patients undergoing peritoneal dialysis compared with linear HRV analysis [34]. In recent years, heart rhythm complexity was extensively studied in many fields, including left heart failure [38], post-infarction myocardial function [39], patients undergoing dialysis [12][34][40], severity of abdominal aorta calcification [41], primary aldosteronism [42], stroke [43], and PH [44]. These studies support the importance of heart rhythm complexity in clinical practice and its potential role in disease risk stratification. In the present study, we demonstrated that heart rhythm complexity parameters, especially MSE scale 5, were significantly associated with PH disease severity and could be used in PH risk stratification. To the best of our knowledge, this is the first study to apply heart rhythm complexity to the prediction of PH disease severity. Although the improvement of the complexity can be attribute to not only the enhanced complexity characteristics but the magnitude of HRV [45], combining different parameters of MSE can give us better information related to the “quality” (complexity) or the “quantity” (magnitude of HRV) changes [46]. Furthermore, model-free complexity can assess the embedded space with variable scales grouped by the K-nearest-neighbor to avoid coarse-graining that may introduce bias due to the fixed dimensions as well as the aliasing filter effect [45][47]. Recently, the local version of the sample entropy was proposed to eliminate the nonstationary effect on the results of complexity analysis [48]. The research by using those new methods warrants further study. In addition, the cardiopulmonary coupling is another important issue in the HRV analysis focusing on the interaction between cardiovascular and cardiorespiratory systems. The cardiorespiratory coupling

between the systems is thought to be with each other in a nonlinear way [49]. MSE has been used to evaluate the cardiorespiratory coupling and the asynchrony. Platiša et al. demonstrated that primary alterations in the regularity of cardiac rhythm resulted in changes in the regularity of the respiratory rhythm in heart failure patients [50]. However, there were limited studies investigating the cardiorespiratory coupling in PH patients. Further studies may be needed to integrate the role of cardiorespiratory coupling in PH patients.

Compared with heart rhythm complexity, linear HRV parameters, including SDRR, SDRR index, VLF, LF/HF ratio, and heart rate turbulence have been widely studied to assess PH [30][51]. Recent studies have also demonstrated an association between impaired linear HRV parameter, SDRR, and PH disease severity markers, including impaired WHO functional status, decreased 6MWD, impaired tricuspid annular plane systolic excursion, right ventricular systolic function, higher TRPG, and NT-proBNP level [52][53][54]. In this study, we first demonstrated a better association between heart rhythm complexity and PH disease severity compared to traditional HRV analysis. Second, the discrimination power of linear HRV for PH disease severity improved significantly after combining heart rhythm complexity parameters. The combination of linear and non-linear HRV parameters to form a new predictive model may have further improved its risk stratification ability and outcome prediction.

There are several limitations to this study. First, this is a pilot study. The number of cases was small, and further studies are needed to validate the results. In addition, model-free complexity analysis or entropy with local characteristics can preserve more information instead of a one-fit-all algorithm. Those methods should be included for a large-scale study to probe the underlying pathophysiological mechanisms related to the changes of the complexity of the PH patients. Second, we only enrolled PH patients in WHO group 1 and group 4, and future studies should enroll different groups of PH patients to investigate the potential application of HRV in these patients. Third, this pilot study is a cross-sectional design and lacks clinical long-term follow-up data. A prospective cohort study with clinical end-point follow-up is needed to confirm the utility of heart rhythm complexity on clinical outcome predictions.

4. Conclusions

This study demonstrated that high-risk PH patients had worse heart rhythm complexity. MSE scale 5 had the best discrimination power to predict high-risk PH patients. Moreover, adding MSE scale 5, area 6–20 or DFAα1 to linear HRV parameters significantly improved the predictive power for high-risk PH patients. Heart rhythm complexity can potentially be used as (i) an indicator of PH disease severity, and (ii) to stratify the risk of PH.

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