VIA MEDICA
ORIGINAL ARTICLE
Cardiology Journal
2009, Vol. 16, No. 6, pp. 553–559

ISSN 1897–5593

Heart rate variability and heart rate turbulence in patients with chronic obstructive pulmonary disease

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Abstract

Background: *In chronic obstructive pulmonary disease (COPD) patients, functional and structural changes of the respiratory system greatly influence cardiovascular autonomic functions. Determining autonomic balance may be important in understanding the pathophysiology of COPD and useful clinically in the treatment of COPD patients. Heart rate variability (HRV) and heart rate turbulence (HRT) are useful tools in assessing the autonomic neurovegetative function. Our aim in this study was to evaluate the HRV and HRT variables in COPD patients. Twenty five moderate to severe COPD patients and 25 healthy subjects were included in this study.*

Methods: *Pulmonary function tests and echocardiographic examination, arterial blood gases analysis were performed, HRV and HRT analysis were assessed from a 24-hour Holter recording.*

Results: *When HRV and HRT parameters were compared, COPD patients had significantly decreased sNN50 total, pNN50, SDANN, SDNN, SDNNI, rMSDD in time domain HRV parameters, and the values of the HRT onset was significantly less negative in COPD patients. Although the values of the HRT slope were lower in COPD patients, there was no significant difference between the two groups. We also found a correlation between HRT and HRV parameters.*

Conclusions: *In addition to HRV parameters, HRT onset was significantly different in COPD patients. In our opinion, the combination of HRV variables and HRT onset may be simple and elegant ways of evaluating cardiac autonomic functions. New investigations of HRT and HRV in COPD patients have a potential importance for improving risk stratification and therapeutic approaches, and understanding the autonomic outcomes of the disease process.* (Cardiol J 2009; 16, 6: 553–559)

Key words: chronic obstructive pulmonary disease, heart rate turbulence, heart rate variability

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Received: 1.05.2009 Accepted: 17.07.2009

Introduction

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous clinical syndrome found in 6–8% of the entire population [1]. In COPD patients, functional and structural changes of the respiratory system deeply influence cardiovascular function [2].

Cardiac arrhythmia and sudden death are common and important causes of mortality in patients with COPD. Several factors such as abnormal autonomic control of cardiopulmonary function may contribute to the development of arrhythmias in these patients [3–6]. Determination of autonomic balance may be important in understanding the pathophysiology of COPD and might be useful clinically in the treatment of patients with COPD [7].

Despite its importance in determining mortality and pathogenesis of the disease there are also some contrary reports about the relation between autonomic dysfunction and COPD [8–12]. It is known that cardiac autonomic functions can be quantified by measuring beat-to-beat variability of the heart rate recorded during 24-hour electrocardiography (ECG) monitoring [13].

Heart rate variability (HRV) analysis has been used as a predictor of sudden cardiac death or as a marker of the progression of cardiovascular disease in several high-risk populations, and it is a useful tool in assessing the autonomic neurovegetative function [13]. Though there are some reports on changes in time-domain and frequency-domain heart rate variability in COPD patients, the information on HRV in patients with COPD has so far been conflicting [8, 11, 14–16]. Heart rate turbulence (HRT), which reflects a response of heart rate to a premature ventricular beat, has been introduced as a new noninvasive tool for risk stratification. The disappearance of HRT implicates the loss of normal autonomic nervous regulation [17]. But no study has until now been published which investigated HRT variables in COPD patients.

The aim of this study was to evaluate the presence of autonomic dysfunction in patients with COPD by HRV and HRT analysis and to determine whether the parameters of HRV and HRT in this population are different from the normal population.

Methods

Patients

Twenty five (22 male, 3 female, mean age: 63 ± ± 7 years) clinically stable, ambulatory, and moderate to severe COPD patients were included in this study. The diagnosis of COPD and its severity were determined according to the GOLD criteria [18]. The control group also consisted of 25 age-matched healthy volunteer subjects (19 male, 6 female, mean age: 60 ± 8 years).

Patients were excluded who were ischemic, had rheumatic heart disease, cardiac failure, diabetes mellitus, thyroid disorders, central or peripheral nervous system diseases and pathologies, electrolyte imbalance, body mass index ≥ 30 kg/m^2, a history of alcohol abuse or taking drugs that affect the heart rate.

The present study was a single center study. All examinations were performed by cardiology and pneumonology outpatient clinics in Izzet Baysal University Hospital from November 2005 to March 2007. The patients and the controls gave their informed consent prior to inclusion in the study. The study protocol was approved by the ethics committee at our institution.

Experimental procedures

Pulmonary function test. All participants underwent spirometric pulmonary function performed in accordance with American Thoracic Society guidelines. Pulmonary function tests were performed by a spirometer (Spirolab MIR, Italy), and force vital capacity (FVC), force expiratory volume 1 (FEV_1), FEV_1/FVC were measured. Arterial puncture was performed only on COPD patients. Arterial blood gases were determined from samples obtained while breathing room air by puncturing the radial artery with the patient seated, and arterial oxygen saturation (SaO_2), PaO_2, $PaCO_2$, pH, and HCO_3 were analyzed. The patients were asked not to take bronchodilators for the 12 hours before the tests. Inhaled corticosteroids were allowed in the same dosage as those already being taken.

Echocardiography. An experienced echocardiographer assessed the echocardiography studies. Echocardiographic examination was carried out with Vingmed Vivid 3 (General Electric, Vingmed Ultrasound, Israel) echocardiographic system equipped with 2.5–3.5 MHz transducers. M-mode and 2-dimensional (2-D) measurements were done in accordance with methods recommended by the American Society of Echocardiography, using all standard echocardiographic windows. Following M-mode and 2-D assessment of morphology, a tricuspid regurgitation systolic jet was recorded from the parasternal or apical window with the continuous-wave Doppler probe. Systolic right ventricular (or pulmonary artery) pressure (PAP) was calculated using the modified Bernoulli equation given by: PAP = 4 × (tricuspid systolic jet)^2 + 10 mm Hg (estimated right atrial pressure). Pulmonary hypertension was defined as a systolic PAP ≥ 35 mm Hg.

Holter analysis. All patients and controls underwent 24-hour Holter monitoring. All patients were in sinus rhythm throughout the recording period. Holter ECGs were analyzed using the Del Mar Reynolds Pathfinder Holter system. One of our authors, blinded to the diagnosis of the patients, conducted the analyses of Holter ECGs.

The HRV analysis was assessed over a 24-hour period and was performed in time domains according to European Society of Cardiology/North American Society of Pacing and Electrophysiology guidelines. The following time-domain parameters were calculated: mean of all normal RR intervals (mean RR); standard deviations of all NN intervals (SDNN); mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording (SDNNI); standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording (SDANN); the square root of the mean of the sum of the squares of differences between adjacent NN intervals (rMSSD); count of the total number of differences between adjacent RR intervals that were greater than 50 ms (sNN50 total); the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals (pNN50).

HRT parameters were calculated according to the original method reported by Schmidt et al. [19] Two numerical descriptors were estimated: turbulence onset reflecting the initial phase of sinus rhythm acceleration and turbulence slope describing deceleration phase. Heart rate turbulence onset (HRT onset) was defined as the difference between the mean of the first two sinus-rhythm RR intervals following the compensatory pause after a premature ventricular complex (PVC) and the mean of the last two sinus-rhythm RR intervals preceding the PVC, expressed as a percentage of the former. Heart rate turbulence slope (HRT slope) was defined as the maximum positive slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after PVC, expressed as ms/beat. The HRT onset or slope was defined as abnormal if the onset was ≤ 2.5 ms/beat.

Patients with atrial fibrillation or without PVC and clinically relevant dysrhythmias or ECG changes potentially interfering with the accurate measurements of HRV and HRT were excluded.

Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA), version 11.0 software for Windows. Descriptive statistics were made and all data was expressed as mean ± standard deviation and percentage ratio. The quantitative values between the two groups were compared using Student's t-test, and the qualitative values were compared using the χ^2 test. Correlations between HRT and HRV parameters and the other parameters such as pulmonary function test and blood gas analysis and echocardiographic results were assessed using Spearman's rank correlation test. P value of < 0.05 was considered statistically significant in all cases.

Table 1. Demographic characteristics and results of respiratory function tests, arterial blood gas analyses of COPD patients and control group.

Variables	COPD (n = 25)	Control (n = 25)	p
Demographic characteristics			
Age (years)	63 ± 7	60 ± 8	0.164
Gender (M/F)	22/3	19/6	0.339
Hypertension (%)	18	16	0.161
BMI [kg/m^2]	24.9 ± 2.9	24.8 ± 3.7	0.577
Smoking (%)	100	64	< 0.001
Pulmonary function test parameters			
FVC (%)	59 ± 15	96 ± 5	< 0.001
FEV_1 (%)	44 ± 15	98 ± 7	< 0.001
FEV_1/FVC	58 ± 9	80 ± 9	< 0.001
Arterial blood gas analysis			
pH	7.40 ± 0.02		
PO_2 [mm Hg]	68 ± 13		
PCO_2 [mm Hg]	41 ± 7		
SaO_2 (%)	91 ± 5		

COPD — chronic obstructive pulmonary disease; BMI — body mass index; FVC — force vital capacity; FEV_1 — force expiratory volume 1; SaO_2 — arterial oxygen saturation

Results

Twenty five (22 male, 3 female, mean age: 63 ± ± 7 years) COPD patients and 25 healthy subjects (19 male, 6 female, mean age: 60 ± 8 years) were included in this study. Age, sex, presence of hypertension, body mass index, prevalence of ventricular premature contraction (VPC), mean heart rate, mean RR were not significantly different between two groups. However, smoking prevalence was significantly higher in COPD patients than in control group. The data are shown in Tables 1 and 2.

There were significant differences in the parameters of pulmonary function test such as FVC, FEV_1 and FEV_1/FVC ratio between COPD patients and the healthy group ($p < 0.001$) as given in Table 1.

Table 2. Comparison of Holter recordings, heart rate variability (HRV) and heart rate turbulence (HRT) parameters between patients with chronic obstructive pulmonary disease (COPD) and control subjects.

Variables	COPD (n = 25)	Control subjects (n = 25)	p
Mean heart rate [beats/min]	73 ± 9	70 ± 8	NS
Mean RR	798 ± 85	764 ± 100	NS
VPC count per day	689 ± 367	283 ± 163	NS
HRT parameters			
HRT onset (%)	–0,010 ± 0.032	–0,165 ± 0.219	0.03
HRT slope [ms/beat]	6.0 ± 3.6	8.1 ± 4.4	NS
Abnormal HRT onset	6 (24%)	3 (12%)	NS
Abnormal HRT slope	2 (8%)	3 (12%)	NS
HRV parameters			
sNN50 total	7965 ± 8320	23875 ± 15917	< 0.05
pNN50 (%)	11.8 ± 9.4	15.7 ± 8.1	< 0.05
SDNN [ms]	111 ± 34	141 ± 25	< 0.001
SDNNI [ms]	51 ± 21	73 ± 16	< 0.01
SDANN [ms]	84 ± 19	120 ± 24	< 0.01
rMSDD [ms]	25 ± 10	60 ± 35	< 0.01

VPC — ventricular premature contraction; SDNN — standard deviations of all NN intervals; SDNNI — mean of the standard deviations of all NN intervals for all 5-minute segments of the entire recording; SDANN — standard deviation of the averages of NN intervals in all 5-minute segments of the entire recording; rMSSD — the square root of the mean of the sum of the squares of differences between adjacent NN intervals; sNN50 total — total count of the total number of differences between adjacent RR intervals that were greater than 50 ms; pNN50 — the number of pairs of adjacent NN intervals differing by more than 50 ms divided by the total number of all NN intervals

On echocardiographic examination, COPD patients had increased right ventricular internal diameter (diastolic), right atrium diameter and PAP compared to controls. However, interventricular wall thickness, left ventricular posterior wall thickness, left ventricular internal diameter (sistolic and diastolic), left atrial diameter, and ejection fraction were similar between COPD patients and controls. The echocardiographic characteristics of the two groups are given in Table 3.

Heart rate variability analysis revealed that COPD patients had decreased sNN50 total, pNN50, SDANN, SDNN, SDNNI, RMSDD in time domain parameters (Table 2).

When HRT parameters were compared, the values of the HRT onset was significantly less negative in COPD patients than the control group (–0.010 ± 0.032 *vs*. –0.165 ± 0.219%, p = 0.03). Although the values of the HRT slope were lower in patients with COPD than the control group, there was no significant difference between the two groups. When dichotomizing patients according to abnormal values (HRT onset > 0% and HRT slope < 2.5 ms/RR) as proposed by Schmidt et al. [19], the number of patients who had abnormal HRT onset and HRT slope were not significantly different between the two groups. Table 2 summarizes the HRT and HRV parameters in COPD and control patients.

Table 3. Comparisons of echocardiographic results of COPD patients and control group.

Variables	COPD (n = 25)	Control (n = 25)	p
IVSd [mm]	10 ± 2	8 ± 3	NS
LVPWd [mm]	11 ± 3	9 ± 2	NS
LVIDd [mm]	53 ± 4	49 ± 6	NS
LVISd [mm]	32 ± 3	30 ± 4	NS
LVEF (%)	64 ± 7	65 ± 7	NS
LA diameter [mm]	34 ± 8	30 ± 9	NS
RA diameter [mm]	36 ± 5	32 ± 7	NS
RV wall thickness [mm]	11 ± 2	7 ± 3	< 0.01
RV diameter [mm]	30 ± 6	21 ± 4	< 0.01
PAP [mm Hg]	32 ± 12	24 ± 6	< 0.01

COPD — chronic obstructive pulmonary disease; IVSd — interventricular septum diastolic diameter; LVPWd — left ventricular posterior wall diastolic diameter; LVIDd — left ventricular internal diastolic diameter; LVISd — left ventricular internal diastolic diameter; LVEF — left ventricular ejection fraction; LA — left atrial; RA — right atrial; RV — right ventricular; LV — left ventricular; PAP — pulmonary artery pressure

When the correlation between HRT and HRV parameters was evaluated, we observed a significant correlation. A negative correlation between HRT onset and SDANN, rMSDD (r = –0.357, p = = 0.011, and r = –0.457, p = 0.001, respectively) and a positive correlation between HRT slope and sNN50 total, pNN50, SDNN, SDANN (r = 0.359,

Table 4. Correlation analysis between heart rate variability (HRV) parameters and heart rate turbulence (HRT) onset, HRT slope.

Parameters	HRT onset		HRT slope	
	r	p	r	p
sNN50 total	–0.201	NS	0.359	0.011
pNN50 (%)	–0.311	NS	0.213	0.002
SDNN [ms]	–0.241	NS	0.355	0.011
SDNNI [ms]	–0.085	NS	0.254	NS
SDANN [ms]	–0.357	0.011	0.320	0.024
rMSDD [ms]	–0.457	0.001	0.210	NS

Abbreviations: see Table 2

p = 0.011; r = 0.213, p = 0.002; r = 0.355, p = 0.011, and r = 0.320, p = 0.024, respectively) were revealed (Table 4).

In addition, we evaluated the correlation between HRT parameters and pulmonary function test (FVC%, FEV_1%, FEV_1/FVC) and arterial blood gas analysis (pH, PO_2, PCO_2, SaO_2) and echocardiographic (especially left ventricular ejection fraction) results. There was only a significant correlation between HRT onset, HRT slope and FEV_1/FVC (r = –0.481, p = 0.017; r = 0.489, p = 0.03, respectively). The correlation between HRT parameters and the other parameters were not significant.

Discussion

Cardiac arrhythmias are common in COPD patients. A poor prognosis has been noted in association with these arrhythmias, particularly ventricular arrhythmias. It is known that cardiac autonomic dysfunction, which is known to be disturbed in COPD patients, is important in the development of arrhythmias. In addition, it is likely that abnormal activity of autonomic nerve innervations can contribute to airway narrowing in COPD, and may be relevant to the pathogenesis of COPD [3, 10, 20–26]. Unfortunately, the actual autonomic tone of the airways is difficult to detect non-invasively in these patients. But it is well known that HRV measurement provides a non-invasive assessment of cardiovascular autonomic functions [13, 27].

By using spectral HRV analysis, Volterrani et al. [8] found that COPD patients had abnormal autonomic nervous function, with, in particular, a depressed HRV response to sympathetic and vagal stimuli. The correction of hypoxemia can partially reverse these abnormalities [9]. In the present study, HRV analysis from 24 hours ambulatory ECG recordings showed that there were marked differences in time domain indices (SNN50 total, pNN50, SDNN, SDNNI, SDANN and rMSDD) between the COPD patients and control groups. These results are consistent with previous observations that autonomic nervous dysfunction exists in COPD [8–10].

The complexity of the pulmonary effects of the autonomic nervous system is considerable, and our knowledge remains elementary, with little known about the prognostic value of HRV in patients with COPD [8, 25].

HRT, a new heart rate derived parameter tracking the response of the heart rate to ventricular arrhythmias, was introduced into electrocardiology in 1999 as a strong predictor of mortality in post-infarction patients, and it can be used as a non-invasive measure of cardiac autonomic dysfunction [19]. The last few years have brought an increasing interest in the analysis of both clinical correlations and the predictive value of this parameter in different subsets of patients. Compared to other non-invasive risk predictors, the relative risk and positive predictive accuracy of HRT are slightly better [17]. But, no study has until now been published which investigated HRT variables in COPD patients.

In our study, in addition to HRV parameters, HRT onset was significantly different in COPD patients. HRT slope was shorter in COPD patients than in control patients. However, this finding did not reach statistical significance, and might result from the number of our cases being relatively low.

Correlations between HRT and HRV parameters have been observed in large populations of patients after myocardial infarction (EMIAT and ATRAMI studies) [28–31]. In one study, HRT slope and HRT onset were found to correlate significantly with almost all heart rate variability time domain parameters, including SDNN, heart rate variability index, TINN, and rMSSD. HRT onset also correlates with pNN50 [32]. Two other studies confirmed a significant correlation between HRT and time domain HRV in patients with diabetes mellitus or dilated cardiomyopathy [33, 34]. In the present study, we also found a negative correlation between HRT onset and SDANN, rMSDD and a positive correlation between HRT slope and sNN50 total, pNN50, SDNN, SDANN. According to our results, HRT parameters were correlated with HRV parameters, indicating that HRT and HRV should be considered as reflections of overall autonomic tone in COPD patients.

As a result, in our opinion, the combination of HRV and HRT (especially HRT onset) variables

may be simple and elegant ways of evaluating cardiac autonomic functions. Such a combination may increase the positive predictivity and lead to a more accurate identification of high risk patients, more aggressive treatment toward preventing sudden death and/or preventing progression of disease to mortality. Therefore, new investigations of HRT and HRV in patients with COPD have a potential importance for improving risk stratification and therapeutic approaches, and understanding the autonomic outcomes of the disease process.

Limitations of the study

This study is a single center, observational and comparative study and the number of cases included is relatively low. Presumably, a larger study population will be necessary to obtain more definite evidence to determine the relationship between HRT, HRV variables and the presence of COPD.

Because our Holter device (Del Mar Reynolds Pathfinder Holter system) analyzes only time domain parameters, we couldn't measure frequency domain parameters of HRV. But it has been mentioned that each of the 24-hour frequency domain spectral measures has an equivalent time domain variable, which is highly correlated with it because both are influenced by the same physiologic inputs and because of mathematical relationships [13, 35].

Acknowledgements

The authors do not report any conflict of interest regarding this work.

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