Original Paper

Cardiovascular Autonomic Dysfunction: A Possible Prognostic Marker in Patients with Arterial Pulmonary Hypertension

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REZUMAT

Neuropatia autonomă cardiovasculară: un posibil marker prognostic la pacienții cu hipertensiune arterială pulmonară

Obiective: Prezentăm rezultatele unui studiu pilot ce și-a propus evaluarea prevalenței neuropatiei autonome cardiace (NAC) și potențialului ei de a deveni un marker de prognostic la pacienți cu insuficiență cardiacă dreaptă secundară hipertensiunii arteriale pulmonare (HTAP). Am investigat corelația dintre NAC, statusul clinic al pacienților și o serie de parametrii paraclinci, precum și implicațiile prognostice ale acestei asocieri.
Material și metodă: Am înrolat 17 pacienți consecutivi cu HTAP, cu evaluarea NAC prin monitorizare Holter ECG/24h cu accent pe analiza turbulenței de ritm sinusal (HRT) și a variabilității de ritm sinusal (HRV) în domeniu timp și domeniu frecvență. S-a efectuat ecocardiografie, cu evidențierea parametrilor specifici cordului drept. Cateterismul de cord drept a fost realizat pentru toți pacienții, cu măsurarea presiunilor de umplere ale ventriculului stâng, presiunii capilare blocate și evaluarea hipertensiunii pulmonare.
Concluzii: Studiul nostru pilot demonstrează că un procent semnificativ de pacienți cu HTAP prezintă semne de NAC și în consecință se află la risc aritmic și de mortalitate înalt, din perspectiva analizei HRT. În consecință, HTAP poate fi asociată cu NAC și această corelație poate avea semnificație predictivă în ceea ce privește morbiditatea și mortalitatea, răspunzând necesității de a găsi noi markeri prognostici pentru evoluția HTAP.

Cuvinte cheie: hipertensiune arterială pulmonară, neuropatie autonomă cardiacă, turbulența de ritm sinusal

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ABSTRACT

Objectives of the study: We evaluated the prevalence of cardiac autonomic neuropathy (CAN) and its potential as a prognostic marker in patients with right heart failure secondary to pulmonary arterial hypertension (PAH) in a pilot study. Furthermore, we investigated its correlation with the clinical status and a series of paraclinical parameters, and prognostic implications of this association.

Methodology: 17 consecutive patients with PAH were evaluated in our study. The evaluation of CAN was realized by Holter ECG/24h monitoring with heart rate turbulence (HRT) and heart rate variability (HRV) analysis in time and frequency domains. Echocardiography was performed with focus on specific right heart parameters. All patients had previously undergone right heart catheterization with measurement of left ventricular filling pressure, pulmonary artery wedge pressure, right heart oxygen saturations and assessment of pulmonary hypertension.

Conclusions: Our pilot study shows that a significant percentage of patients with PAH exhibit signs of CAN and are at high arrhythmic and mortality risk, from the standpoint of HRT analysis. Consequently, pulmonary hypertension can be associated with CAN, and this correlation can have morbidity and mortality implications, thus answering the need for a new prognostic marker in the evolution of PAH.

Key words: pulmonary arterial hypertension, cardiac autonomic neuropathy, heart rate turbulence

INTRODUCTION

In the past two decades, the association between the cardiovascular autonomic dysfunction and the cardiovascular mortality has been well documented. This association indicates that individuals with abnormal autonomic function tests are candidates for close surveillance. In type 2 diabetes it is recommended that a baseline determination of cardiovascular autonomic function be performed upon diagnosis and within 5 years of diagnosis for those with type 1 diabetes, followed by a yearly repeat test. [1]

Out of the markers that objectify this relationship, heart rate variability (HRV) has proven to be the most reliable and the easiest to quantify. Although HRV has been the subject of numerous clinical studies whose purpose was linking heart rate changes to the gravity and the evolution of the disease, only in two clinical settings a consensus was reached. The drop in HRV can be used as a risk factor in the period following an acute myocardial infarction (AMI) and as a warning sign for cardiac autonomic neuropathy (CAN) in diabetic patients. HRV parameters and their possible prognostic significance have not been thoroughly evaluated in patients presenting pulmonary arterial hypertension.

Objective

We set to evaluate the prevalence of CAN and its potential as a prognostic marker in patients with right heart failure secondary to pulmonary arterial hypertension (PAH) in a pilot study. Furthermore, we investigated its correlation with the clinical status and a series of paraclinical parameters, and prognostic implications of this association.

MATERIAL AND METHOD

17 consecutive patients with PAH were evaluated in our study. Patients were referred to our cardiology ward from the "Marius Nasta" Institute of Pneumology, and were all included in the National Program for Arterial Pulmonary Hypertension Management.

The evaluation of CAN was realized by Holter ECG/24h monitoring with heart rate turbulence (HRT) and HRV analysis in time and frequency domains. A Cardiospy Holter ECG was used (software: Cardiospy V4.04.RC13b).

HRT is the physiologic response of the sinus node at a ventricular extrasystole, and it is defined by calculating 2 parameters: turbulence onset (TO) and turbulence slope (TS).

The term HRT describes short-term fluctuations in sinus cycle length that follow spontaneous ventricular premature complexes (VPCs) (2). TO was defined as the difference between the mean of the first 2 sinus RR intervals preceding the ventricular premature complex (VPC) and the mean of the subsequent two sinus RR intervals, expressed as a percentage. TS was defined as the maximum positive

value of the slope of a regression line assessed over any sequence of five subsequent sinus-rhythm RR intervals within the first 20 sinus-rhythm intervals after VPC. If more than one positive slope occurred in this period, the first positive slope was used. The value of TS was expressed in milliseconds per RR interval.

In normal subjects, sinus rate initially briefly accelerates and subsequently decelerates compared with the pre-VPC rate, before returning to baseline (2) (Fig. 1).

The TO and TS variables can be used as separate clinical variables or in a combination. In risk stratification studies, HRT values are usually classified into 3 categories: 1) HRT category 0 means TO and TS are normal; 2) HRT category 1 means 1 of TO or TS is abnormal; and 3) HRT category 2 means both TO and TS are abnormal. If HRT cannot be calculated because no or too few suitable VPC tachograms are found in the recording, patients who are otherwise in sinus rhythm are classified as HRT category 0.

In most clinical studies, however, TO $<0\%$ and TS >2.5 ms/R-R interval are considered normal. These originally proposed cutoff values were validated in the data of 3 large post-infarction studies (totalling 2,646 patients) (3, 4)

Patients with supraventricular arrhythmias such as atrial fibrillation and atrial flutter were excluded from the study.

Echocardiography was performed (using a GE Vivid 7 machine) with focus on specific right heart parameters. Echocardiography was performed in all patients, with focus on right ventricular (RV) function and parameters: right atrium (RA), RV, pulmonary artery (PA) dimensions; tricuspid annular plane systolic excursion (TAPSE); RV/RA tricuspid regurgitation gradient with inferior vena cava dimensions and indirect evaluation of systolic pulmonary artery pressure (PAPs); ascension time of velocity in pulmonary valve; RV ejection fraction (EF) in 3D; presence of pericardial effusion.

All patients had previously undergone right heart catheterization with measurement of left ventricular filling pressure, pulmonary artery wedge pressure, right heart oxygen saturations and assessment of pulmonary hypertension.

RESULTS

There were 17 patients with arterial pulmonary hypertension included in the study, with the following gender distribution: 64.71% females, 35.29% males. Mean age was 53.4 years (age range 37 – 74 years old). At the moment of inclusion in the study, the patients had been diagnosed with PAH for a mean age of 3.14 years (range: 2 months to 51 months since first diagnose).

There was Holter ECG/24h monitoring on all patients, with HRT analysis: 76.47% of the patients have abnormal TO, while 64.7% have abnormal TS. Mean TS was 6.27 (range 0.1 – 31.5). Patients were divided in 3 categories: HRT category 0 with normal
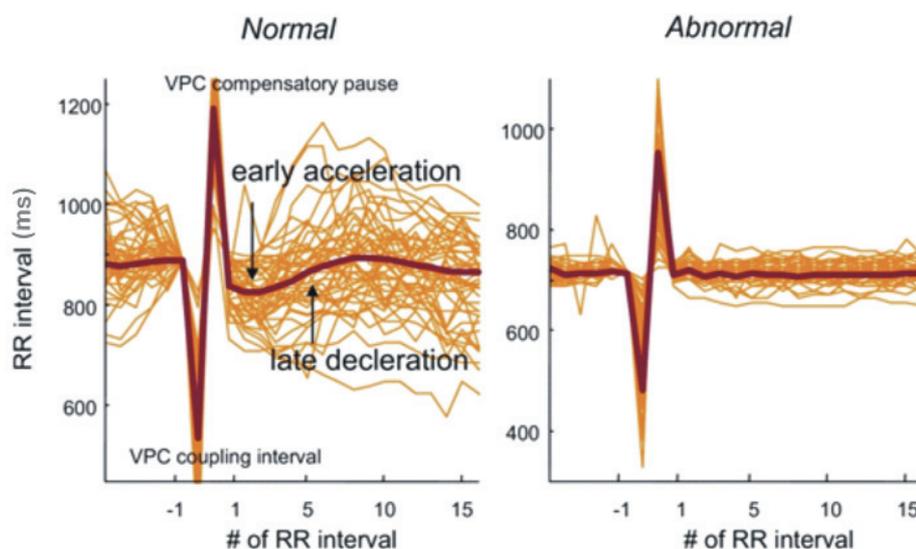
Figure 1. Ventricular premature complex (VPC) tachograms showing normal (left) and abnormal (right) heart rate turbulence (HRT) (2)
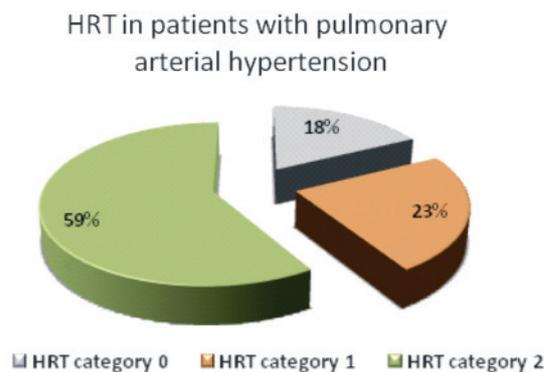
Figure 2. Distribution of patients with PAH according to heart rate turbulence categories

TO and TS, HRT category 1 with abnormal either TO or TS, HRT category 2 both TO and TS abnormal (**Fig. 2**).

Mean RV/right atrium (RA) gradient was 61.14 mmHg (range 26-129 mmHg). Mean TAPSE was 18.92 mm (range 10-26 mm), while mean pulmonary ascension time (AT) was 53.64 ms (range 34-90 ms). Mean RV dimension from a right ventricle-focused apical 4-chamber view at mid-level was 49.21 mm (range 38-62 mm).

The follow-up of the patients was performed over a period of 24 months with 2 of the patients being lost to follow-up. Out of the patients that were included in HRT category 2, 33.3% had died. None of the patients from HRT categories 0 and 1 had died at 24 months.

As far as treatment was concerned, 5 patients (29.41%) were treated with endothelin receptor antagonists, 7 patients (41.17%) were treated with sildenafil, and 5 patients (29.41%) were treated with bitherapy, endothelin receptor antagonists and sildenafil. During the 24 months of follow-up, one patient has undergone lung transplantation.

DISCUSSION

Pulmonary arterial hypertension (PAH) is a fatal disease that has no satisfactory predictive model of survival (6). Although 6-minute walk distance (6MWD) and other end points are considered potential surrogates for survival of patients with PAH, they have never been thoroughly tested for their predictive abilities. However, these factors are often used to make critical decisions about the utility and efficacy of present-day therapeutic means (7).

This gap in adequate evaluation of PAH patients warrants the search for new prognostic tools, such as HRV.

In advanced chronic heart failure (CHF), correlation between heart rate variability (HRV) and parameters of disease severity is still unclear. A reduced HRV has been related to left but not to right ventricular function parameters (5). Lucreziotti et al have shown that spectral analysis of HRV, calculated from short electrocardiographic recordings, may represent a simple but effective means contributing to risk stratification of patients with severe CHF. Autonomic information obtained from this analysis suggests that right ventricular dysfunction may be a critical element determining autonomic imbalance in patients with severe CHF (5).

HRT is the newest non-invasive ECG risk predictor, with proven clinical utility in evaluating sudden cardiac death post AMI. On these patients, the third HRT category is associated with the lowest survival rate, being a powerful invariable predictor of death rate in all cases. However, data on the predictive value of HRT for mortality in patients with heart failure are limited.

Monitoring heart rate behaviour and response is especially important for CHF patients because early autonomic nervous system dysfunction and neuro-hormonal activation play a dominant role in the progression and prognosis of this disease [8,9]. CHF is characterized by an autonomic imbalance with impaired vagal activity and increased sympathetic activity. Impaired vagal activity is associated with increased mortality [8,10] and consequently assessment of vagal function is important in CHF. HRT is considered to be a vagally mediated phenomenon, non-invasively reflecting baroreflex sensitivity, which is frequently impaired in patients with CHF [8,11]. Blunted HRT has been observed in patients with cardiomyopathies regardless of the underlying etiology (13).

Moore et al. reported that TS is an independent predictor of death due to decompensated heart failure in ambulant heart failure patients [8,12]. Moreover, Cygankiewicz et al. reported that abnormal TS and HRT category 2 were independently associated with increased all-cause mortality, sudden death, and heart failure death after adjustment for clinical covariates in multivariate analysis [8,13]. However, most of available data is derived from patients with left-sided heart failure.

In patients with pulmonary hypertension, the

inclusion of 59% of the subjects in the third HRT category can be associated with high arrhythmic risk and mortality, similar to findings in other cohorts of patients with CAN. In our study group, follow-up at 24 months documented a 33.3% (3 out of 9 patients) mortality in the HRT 2 group as opposed to no deaths in the HRT 0 and 1 categories.

Inclusion of these patients in the HRT categories did not correlate with current NYHA functional class or with echocardiographic parameters of RV function. This finding implies that a potential validation of HRT as a prognostic factor can be done independent of other prognostic tools. Due to the small patient group, no correlations were possible between treatment and HRT parameters.

Validating the HRT's quality as a prognostic marker in PAH would require an adequate longer follow-up.

Study limitations

Absence of long-term follow-up and the relatively small patients group represent the limits of this study. Furthermore, the patients with atrial fibrillation were excluded, because HRT could not be determined in the presence of atrial fibrillation.

CONCLUSIONS

Our pilot study shows that a significant percentage of patients with arterial pulmonary hypertension exhibit signs of CAN and are at high arrhythmic and mortality risk, from the standpoint of HRT analysis. All deaths in the study group in the first 24 months after inclusion occurred in patients placed in the high risk HRT category. Consequently, pulmonary hypertension can be associated with cardiac autonomic neuropathy, and this correlation can have morbidity and mortality implications, thus answering the need for a new prognostic marker in the evolution of PAH.

Acknowledgement

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