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Impaired cardiac autonomic control relates to disease severity in pulmonary hypertension

Roland Wensel MD PhD[1,2]*, Clemens Jilek MD[1,3,]*, Marcus Dörr MD[4], Darrel P Francis MD[2], Helmut Stadler[1], Tobias Lange MD[1], Friedrich Blumberg MD[1,5], Christian Opitz MD[6], Michael Pfeifer MD[1,7] and Ralf Ewert MD[4]

*The first two authors should be regarded as joint first authors.

1.) Department of Internal Medicine II, Universtätsklinikum Regensburg, Germany
2.) International Centre for Circulatory Health, National Heart & Lung Institute, Imperial College London, UK.
3.) Deutsches Herzzentrum München, Klinik der Technischen Universität München, Germany
4.) Department of Internal Medicine B, Ernst-Moritz-Arndt University Greifswald, Germany
5.) Department of Internal Medicine, Prosper-Hospital, Recklinghausen, Germany
6.) Department of Internal Medicine/Cardiology, DRK Kliniken Berlin Köpenick, Germany
7.) Center for Pneumonology, Donaustauf Hospital, Donaustauf, Germany

Address for correspondence:

Dr Roland Wensel, International Centre for Circulatory Health, St Mary's Hospital and Imperial College, 59 North Wharf Rd, London, UK; Email: rolandwensel@web.de

Short title:

Autonomic control in pulmonary hypertension

Abstract

Pulmonary arterial hypertension (PAH) results in chronic right heart failure which is associated with an increase in sympathetic tone. This may adversely affect cardiac autonomic control. We investigated the changes in cardiac autonomic nervous activity in relation to disease severity in patients with PAH.

In 48 patients with PAH (median WHO class III, pulmonary artery pressure 52±14 mmHg, pulmonary vascular resistance 1202±718 dyne·s^{-1}·cm^{-5}, cardiac index 2.0±0.7 L·min^{-1}·m^{-2}) and 41 controls cardiac autonomic nervous activity was evaluated by measurement of heart rate variability (HRV) and baroreflex sensitivity. All patients underwent cardiopulmonary exercise testing (peakVO_2 13.2±5.1 mL·kg^{-1}·kg^{-1}, VE/VCO_2-slope 47±16).
In patients with PAH spectral power of HRV was reduced in the high-frequency (239±64 vs. 563±167 ms^2), low-frequency (245±58 vs. 599±219 ms^2) and very low-frequency band (510±149 vs. 1106±598 ms^2, all $p<0.05$). Baroreflex sensitivity was also blunted (5.8±0.6 vs. 13.9±1.2 ms/mmHg, $p<0.01$). The reduction in high-frequency ($r=0.3$, $p=0.04$) and low-frequency ($r=0.33$, $p=0.02$) spectral power and baroreflex sensitivity ($r=0.46$, $p<0.01$) was related to the reduction in peak oxygen uptake.

Patients with PAH have a marked alteration in cardiac autonomic control that is related to exercise capacity and may therefore serve as an additional marker of disease severity.

Key words

heart autonomic system, exercise capacity, heart rate variability, pulmonary hypertension

Introduction

Pulmonary arterial hypertension (PAH) is a rapidly progressive disease leading to right heart failure and death [1]. The increasing availability of medical therapy has substantially improved symptoms and prognosis [1]. In the decision process on initiation and escalation of treatment risk stratification of the patients plays a major role. In this regard there is increasing awareness that chronic right heart failure is a syndrome that affects many organ systems including neuroendocrine system [2], [3], [4] renal function [5] and that these secondary changes are marker of disease severity progression and prognosis. Current evaluation of disease severity is based on measurement of resting haemodynamics [6], exercise capacity [7] and neurohormonal markers [2], [3], [4].

PAH is associated with in increased sympathetic tone as assessed by muscle sympathetic nerve activity, whereas there are conflicting data regarding plasma catecholamine levels [8], [9]. The increased sympathetic tone seems to be related to the haemodynamic abnormalities.

In left heart failure chronic sympathetic overactivity leads to an impairment of cardiac autonomic nervous activity with reduced baroreflex sensitivity (BRS) and altered heart rate variability (HRV) [10]. The altered autonomic tone is associated with and potentially also a mediator of impaired prognosis in these patients [11], [12], [13].

In animal models of monocrotaline-induced pulmonary hypertension reduction in spectral power of HRV has been observed [14]. Changes in spectral distribution of HRV with reduction of low frequency and high frequency power [15] and increased low-frequency vs. high-frequency spectral power ratio (LF/HF ratio) have been described in patients with PAH [16]. These changes were partially reversible on treatment with subcutaneous treprostinil. This led to the hypothesis

that in patients with PAH there is an alteration in cardiac autonomic nervous activity, which may also relate to disease severity.

We, therefore, set out to characterize the cardiac autonomic nervous activity and its relation to exercise capacity as a marker of disease severity in patients with symptomatic PAH.

Methods

Patients

We studied 48 patients with PAH (idiopathic PAH n=36, PAH associated with congenital heart defects n=4, PAH associated with connective tissue disease n=8; 13 male, age 51 ± 12 years). Patients were in median WHO class III. Haemodynamic assessment showed a marked degree of pulmonary hypertension and reduced cardiac index (mean pulmonary artery pressure 52 ± 14 mmHg, pulmonary vascular resistance 1202 ± 718 dyne·s^{-1}·cm^{-5}, cardiac index 2.0 ± 0.8 L·min^{-1}·m^{-2}). Chronic medication included Endothelin-1 receptor antagonists (n=29), phosphodiesterase type V inhibitors (n=2), inhaled iloprost (n=7), intravenous iloprost (n=5), oral beraprost (n=4), calcium channel antagonists (n=2), oral anticoagulation (n=37), spironolactone (n=16), loop diuretics (n=32) and digoxin (n=3).

Subjects

Forty-one age and gender matched healthy individuals (12 male, age 48 ± 13 years, heart rate 69±10 min^{-1}) served as control group for measurements of heart rate variability and baroreflex

sensitivity. All subjects had no history of a medical illness, a normal physical examination and none of them was taking any medication.

The study complies with the Declaration of Helsinki and has been approved by the institutional ethics committee. Informed consent has been obtained from all patients.

Measurements

Cardiopulmonary exercise testing

All patients underwent cardiopulmonary exercise testing. The exercise test was done on a treadmill in 26 patients and with a cycle ergometer in 22 patients. The modified Naughton protocol for treadmill exercise testing was used. Exercise testing with the use of a cycle ergometer (ER 900; Jäger, Würzburg, Germany) was started at 20 W with a stepwise increment of 16 W/min. Oxygen uptake (VO_2), carbon dioxide output (VCO_2), instantaneous expiratory gas concentrations throughout the respiratory cycle, and minute ventilation (VE) were measured continuously on a breath-by-breath basis (Oxycon, Jaeger-Viasys, Germany).
Peak VO_2 was defined as the oxygen uptake that was measured at peak exercise, which always occurred well beyond the anaerobic threshold. The VO_2 at the gas exchange anaerobic threshold was detected with the V-slope method [17], supplemented by the simultaneous observation of end-tidal gas concentrations. Pulmonary gas exchange was assessed by the VE/VCO_2-ratio and the slope of this relationship on exercise (established as reported previously [18]). Heart rate and blood pressure (by sphygmomanometer) were measured at rest and during each stage of exercise.

HRV and Baroreflex sensitivity

Patients and controls were studied between 1:00 PM and 5:00 PM under standardized conditions, in a quiet air-conditioned room. Before data acquisition, all patients were in the fasting state for at least 2 hours and were not allowed to smoke or drink alcohol- or caffeine-containing beverages for 24 hours. Subjects rested supine for 15 minutes and then underwent 2 successive investigations: one continuous 20 minute recording at rest and one 5 minute recording during controlled breathing at 0.1 Hz by following a sinusoidal visual and auditory signal [19]. During each investigation, RR interval, blood pressure (BP) and respiration were recorded. Procedures were performed in the same order in all subjects. BP was measured by a tonometric device (CBM 7000; Colin, USA), with the pressure probe place over the right radial artery, the wrist resting comfortably at the level of the heart. ECG was acquired from the limb lead with the largest R wave (Sirekust732, Siemens, Germany). Respiratory rate was measured by thoracic impedance (Sirekust732, Siemens, Germany). All data were sampled at 1000 Hz on a computer using an analogue-to-digital converter (National Instruments, USA). Readings were saved and analyzed off-line with custom designed software. The program measured RR intervals and beat-to-beat systolic pressure while ectopic beats were excluded by linear interpolation [19].

Heart Rate Variability

HRV analysis was made on 20 minute ECG recordings and time domain and frequency domain indexes were calculated using our laboratory's software. The following frequency domain indices were assessed:

- VLF: Very low frequency power (0.0033–0.04 Hz)

- LF: Low frequency power (0.04–0.15 Hz)

- HF: High frequency power (0.15–0.4 Hz)

Baroreflex Sensitivity

For BRS assessment, we measured average amplitudes of oscillations in RR interval and in systolic blood pressure (SBP). BRS was assessed non-invasively by the following methods [20]:

BRS Frequency domain index

- α-LF: Square root of the ratio between RR and SBP Power spectral analysis was performed on the RR interval and SBP data using an autoregressive algorithm [19],[21]. The α-index (αLF) was calculated in the presence of an adequate coherence (>0.5) between the RR interval and SBP as assessed by cross-spectral analysis.

BRS Sequence method

- BRSseq: The average value of the individual linear correlation slopes between RR and SBP during sequences in which RR and SBP concurrently increased or decreased over three or more beats. The minimum change required was 1 mm Hg for SBP and 4 ms for RR interval. The regression

slope was calculated in those sequences with correlation coefficients of >0.8.

BRS during controlled breathing

- BRScbr — The ratio of the average amplitude of oscillation in RR to the average amplitude of oscillations in SBP during a 5 min interval of controlled breathing [19]. The resultant RR and SBP signals were processed with a simple time-domain digital filter to extract the signal component at the frequency of interest (0.1 Hz).

Statistical analysis

Data are presented as mean ± standard deviation. Indices with skewed distribution were log-transformed. Data were analyzed with Sigma Stat 3.0 (SPSS, Chicago, Ill). Differences between patients and controls were analyzed with an unpaired t-test or the Mann-Whitney test if data did not follow a normal distribution. The relationship between two variables was tested using the Pearson correlation. A p-value < 0.05 was considered significant.

Results

Cardiopulmonary exercise testing

The CPET-results of the patients with PAH are presented in table 1. In 15 patients the oxygen uptake at the anaerobic threshold could not be determined because of very low exercise capacity. Seven patients showed a pattern of pulmonary gas exchange consistent with a right-to-left shunt

during exercise [22] which resulted in a nonlinear Ventilation/CO_2-production relationship. In these patients VE/VCO_2-slope was not calculated.

Table 1. Results of cardiopulmonary exercise testing of PAH patients

Parameter	
Exercise duration, sec	384 ± 33
SBP rest, mmHg	121 ± 3
DBP rest, mmHg	76 ± 2
SBP peak exercise, mmHg	150 ± 6
DBP peak exercise, mmHg	83 ± 3
Oxygen uptake at anaerobic threshold, $mL \cdot kg^{-1} \cdot min^{-1}$ (n=33)	10.4 ± 1.1
Peak oxygen uptake, $mL \cdot kg^{-1} \cdot min^{-1}$	13.2 ± 5.1
RER at peak exercise	1.03 ± 0.05
VE/VCO_2 rest	46 ± 1
$petCO_2$ rest, mmHg	26.1 ± 0.7
VE/VCO_2-slope (n=40)	47 ± 16
SaO_2 rest, %	92 ± 1
SaO_2 peak exercise, %	87 ± 1

SBP, systolic blood pressure; DBP, diastolic blood pressure; RER, respiratory exchange ratio; VE/VCO_2, ventilation to CO_2 output ratio; $petCO_2$, endtidal partial pressure of CO_2; SaO_2, arterial oxygen saturation.

Heart rate variability and Baroreflex sensitivity

Patients with PAH showed a reduction in total power of heart rate variability (962 vs. 1938 ms^2, $p<0.001$) analyzed in all spectral bands when compared to healthy controls (Figure 1). However, there was no significant difference in the LF/HF-ratio (1.28 vs. 1.04, p=0.19). As shown in figure 2, baroreflex sensitivity was consistently decreased in patients with PAH.

Relation of heart rate variability to exercise capacity and pulmonary gas exchange

The reduction of both HF and LF-power was associated with progressive impairment of exercise capacity as assessed by peak oxygen uptake (Figure 3). However, there was no significant correlation with the impairment of ventilatory efficiency (logHF vs. VE/VCO_2-slope r=-0.13, p=0.4; logLF vs. VE/VCO_2-slope r=-0.22, p=0.14).

Relation of Baroreflex sensitivity to exercise capacity and pulmonary gas exchange

Baroreflex sensitivity assessed by the controlled breathing method (Figure 4) and the αLF-index revealed a significant correlation with peak oxygen uptake (r=0.46, $p<0.01$ and r=0.36, $p<0.05$, respectively). No significant correlation with the VE/VCO_2-slope was found (r=-0.13, p=0.4).

Discussion

Pulmonary arterial hypertension results in chronic right heart failure which is not just a condition of pure haemodynamic failure but a syndrome affecting many organ systems.

Increased sympathetic activity as evident from increased systemic vascular resistance [23] or direct measurement of sympathetic nervous activity [8] may have detrimental effects on disease

progression that parallel those seen in chronic left heart failure. However, little is known about such consequences of sympathetic overactivity in PAH.

Our study shows that in patients with PAH chronic sympathetic overactivity leads to profound changes in cardiac autonomous regulation and that these changes relate to disease severity.

Heart rate variability

We assessed HRV based on 20 minute resting ECG recordings under standardized external conditions. This duration of measurement allows ample time for the frequencies of interest. Compared to 24 hour recording this carries the advantage of eliminating variation in physical activity between patients that inevitably occurs during unrestricted and unobserved behavior.

We observed a marked reduction in the total power of heart rate variability with similar reduction of HF, LF and VLF power compared to healthy controls.

Since heart rate variability in the HF-band is mediated by the vagal activity, our findings indicate vagal withdrawal, which can be explained by the underlying cardiac failure. The observed reduction in the LF-power, which is mainly regulated by sympathetic innervation, may at first be surprising. Sympathetic stimulation that results from physiologic changes (i.e. orthostasis, exercise, cold exposure) or acute and subacute disease (i.e. post myocardial infarction) increases LF-power compared to total and HF-power [20], [11]. In contrast, chronic sympathetic stimulation, as in chronic left heart failure, leads to a reduction in LF-power indicating a reduced susceptibility to respond to changes in sympathetic tone [12], [13]. This suggests that the

reduction in LF-power in PAH patients results from chronic sympathetic activation that has been reported previously [8]. The concomitant changes in HF and LF-power explain the absence of a significant change in the LF/HF-ratio compared to healthy controls. Fauchier et al. [15] described much higher LF/HF for patients with PAH but for normal individuals as well. However, they used 24 hour ECG recordings and their finding might be explained by higher physical activity during the sampling period.

Baroreflex sensitivity

We used three different non-invasive methods to assess BRS and consistently observed a marked reduction in BRS. These results fit perfectly in the observed changes in HRV:

First, the baroreflex consists of a reciprocal change in heart rate and systemic vascular resistance in response to spontaneous changes in arterial blood pressure (BP) [24]. The afferent pathway involves parasympathetic fibres of the vagal and glossopharyngeal nerve. The efferent pathway involves both sympathetic (which is reduced when BP rises) and vagal outflow (which is increased when BP rises). A blunted BRS therefore contributes to reduced vagal outflow and unrestricted sympathetic outflow to the heart, which is reflected by the changes in LF and HF-power.

Second, the LF-band has been suggested to reflect the baroreflex induced changes in heart rate and reduced BRS therefore results in reduced LF-power [25],[26].

What is the cause of altered cardiac autonomous activity in PAH?

Chronic sympathetic overactivity, which has been described in PAH is a likely cause of the change in autonomous control. The data from Ciarka et al. [9] suggest that sympathetic activity is directly related to the severity of the underlying haemodynamic failure with increased right atrial pressures and low cardiac output in PAH. On the other hand, the changes in cardiac autonomic nervous activity observed in our study parallel those seen in patients with chronic left heart failure [10], [12] but also other chronic cardiac conditions that are associated with relative circulatory failure for example in adults with congenital heart defects [27], [28]. This suggests that the chronic autonomic imbalance and its effects on cardiac autonomous nervous activity is a nonspecific response to chronic circulatory/heart failure regardless of its origin. Furthermore, data from patients with praedominant left heart failure also suggest that peripheral changes that occur secondary to the underlying haemodynamic disorder are major contributors to increased sympathetic activity [21], [29]

In chronic left heart failure peripheral blockade of sympathetic overactivity improves cardiac function, symptoms and prognosis and is therefore an integral part of medical therapy [30]. Is there a role for such therapy in patients with PAH? Currently, there do not exist any controlled data on this issue, nevertheless beta-blockade is usually badly tolerated in PAH and may lead to acute decompensation of right heart failure even when administered at minute doses (MM Hoeper, personal communication). This difference to left heart failure may be explained by the chronic unrelieved pressure overload of the right ventricle that requires chronic inotropic support by sympathetic stimulation. However, this may change with further improvement of medical therapy aiming to reverse pulmonary vasculopathy.

CANA in relation to exercise capacity and pulmonary gas exchange

We found a severely reduced peakVO_2 and ventilatory efficiency (assessed by VE/VCO_2-ratio or VE/VCO_2-slope) in our patients, which is consistent with previous reports in PAH [31], [32], [23]. In our study the alteration in cardiac autonomic modulation was related to disease severity as measured by peak oxygen uptake. Hence it can be concluded that cardiac autonomous control is related to disease severity in PAH. However, no significant relationship between parameters of ventilatory efficiency and CANA was found. This is a surprising finding since VE/VCO_2 ratio and slope have consistently been shown to be increased in PAH [31], [32], [23]. A potential explanation to this is that VE/VCO_2-slope does depend on patient's effort if all exercise data are included in the regression analysis. In fact, the mean peak respiratory exchange ratio was relatively low in our study, which might imply that VE/VCO_2-slope was measured falsely low in some patients. This would confound the relationship between VE/VCO_2-slope and CANA.

Measurement of HRV and BRS are non-invasive and entirely free of any inconvenience to the patient. They can therefore be obtained and repeated at any stage of disease. This implies a potential role of these measurements in risk stratification and treatment effects in PAH. However, this has to be investigated by further studies.

Study limitations

It is a potential limitation of our study that we did not directly measure sympathetic outflow itself. Direct measurement by muscle sympathetic nerve activity, which is a difficult and sometimes uncomfortable procedure, is recognized to show increased sympathetic activity that relates to disease severity in PAH. Potentially more accessible indices such as plasma catecholamine levels are unfortunately not reliable at reflecting sympathetic status in PAH [8]. However, the current study did not aim to measure sympathetic activity, which has been shown to be increased in PAH previously [8], [9], but to investigate the effect on cardiac autonomous control and its relation to disease severity. We therefore took a pragmatic and approach of making measurements by methods that patients found acceptable, and are likely to reflect cardiac autonomic nerve function.

The patients in this study have been suffering from PAH including IPAH, PAH related to connective tissue disease and PAH related to congenital heart defects. It therefore is possible that our results have been confounded by the underlying disease (i.e. connective tissue disease). However, the presence of PAH seems to have a major adverse effect on symptomatology and prognosis of such patients [33]. In fact, any clinical measure of disease severity (i.e. WHO functional class, six minute walk test or peak oxygen uptake) reflect an integral measure that is influenced by PAH but comorbidities as well. Because of the small number of patients with underlying connective tissue disease we are unable to comment on the relationship between autonomic control and pulmonary gas exchange variables. Exclusion of the non-IPAH patients, however, did not significantly alter the results of our study.

For logistic reasons we had to use different exercise protocols (treadmill vs. bicycle) on the two study sites, which may have confounded our results. This would, however, would have made

more unlikely to find a relationship between peakVO_2 and autonomic control and should not biased the study towards a false positive finding. Furthermore, the difference in peakVO_2 in PAH patients seems to be very small when different exercise protocols were used [34].

Finally, although none of the patients has been treated with a beta-blocker, medication may have influenced our measurements of CANA. There are data to suggest effects of Endothelin-1 antagonism, digoxin and prostanoids on autonomic function [35], [36], [37], which may confound the correlation of measures of CANA and disease severity. This should be taken into account in particular if serial measurements are taken with overlapping changes in medication.

Conclusion

In patients with PAH there is profound alteration of cardiac autonomic control. The observed changes parallel those seen in chronic left heart failure and relate to disease severity. Measurement of cardiac autonomic function may have a role in clinical assessment and risk stratification of patients with PAH.

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References:

1. Thenappan T, Shah SJ, Rich S, Gomberg-Maitland M. A USA-based registry for pulmonary arterial hypertension: 1982-2006. *Eur Respir J* 2007; 30:1103-10.

2. Nootens M, Kaufmann E, Rector T, Toher C, Judd D, Francis GS, Rich S. Neurohormonal activation in patients with right ventricular failure from pulmonary hypertension: relation to hemodynamic variables and endothelin levels. *J Am Coll Cardiol* 1995; 26:1581-5.

3. Sakamaki F, Satoh T, Nagaya N, Kyotani S, Oya H, Nakanishi N, Kuribayashi S, Ishida Y. Correlation between severity of pulmonary arterial hypertension and 123I-metaiodobenzylguanidine left ventricular imaging. *J Nucl Med* 2000; 41:1127-33.

4. Leuchte HH, El Nounou M, Tuerpe JC, Hartmann B, Baumgartner RA, Vogeser M, Muehling O, Behr J. N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension. *Chest* 2007; 131:402-409.

5. Shah SJ, Thenappan T, Rich S, Tian L, Archer SL, Gomberg-Maitland M. Association of serum creatinine with abnormal hemodynamics and mortality in pulmonary arterial hypertension. *Circulation* 2008; 117:2475-2483.

6. Galiè N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, Olschewski H, Peacock A, Pietra G, Rubin LJ, Simonneau G, Priori SG, Garcia MA, Blanc JJ, Budaj A, Cowie M, Dean V, Deckers J, Burgos EF, Lekakis J, Lindahl B, Mazzotta G, McGregor K, Morais J,

Oto A, Smiseth OA, Barbera JA, Gibbs S, Hoeper M, Humbert M, Naeije R, Pepke-Zaba J; Task Force. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. *Eur Heart J* 2004; 25:2243-2278.

7. Hoeper MM, Markevych I, Spiekerkoetter E, Welte T, Niedermeyer J. Goal-oriented treatment and combination therapy for pulmonary arterial hypertension. *Eur Respir J* 2005; 26:858-863.

8. Velez-Roa S, Ciarka A, Najem B, Vachiery JL, Naeije R, van de Borne P. Increased sympathetic nerve activity in pulmonary artery hypertension. *Circulation* 2004; 110:1308-1312.

9. Ciarka A, Vachièry JL, Houssière A, Gujic M, Stoupel E, Velez-Roa S, Naeije R, van de Borne P. Atrial septostomy decreases sympathetic overactivity in pulmonary arterial hypertension. *Chest* 2007; 131:1831-1837.

10. Eckberg DL, Drabinsky M, Braunwald E. Defective cardiac parasympathetic control in patients with heart disease. *N Engl J Med* 1971; 285:877-883.

11. Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Decreased heart rate variability and its association with increased mortality after acute myocardial infarction. *Am J Cardiol* 1987; 59:256-262.

12. van de Borne P, Montano N, Pagani M, Oren R, Somers VK. Absence of low-frequency variability of sympathetic nerve activity in severe heart failure. *Circulation.*1997; 95:1449-1454.

13. Ponikowski P, Anker SD, Chua TP, Szelemej R, Piepoli M, Adamopoulos S, Webb-Peploe K, Harrington D, Banasiak W, Wrabec K, Coats AJ. Depressed heart rate variability as an independent predictor of death in chronic congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. *Am J Cardiol* 1997; 79:1645-1650.

14. Sanyal SN, Ono K. Derangement of autonomic nerve control in rat with right ventricular failure. *Pathophysiology* 2002; 8:197-203.

15. Fauchier L, Babuty D, Melin A, Bonnet P, Cosnay P, Paul Fauchier J. Heart rate variability in severe right or left heart failure: the role of pulmonary hypertension and resistances. *Eur J Heart Fail* 2004; 6:181-185.

16. Rosas-Peralta M, Sandoval-Zárate J, Attie F, Pulido T, Santos E, Granados NZ, Miranda T, Escobar V. Clinical implications and prognostic significance of the study on the circadian variation of heart rate variability in patients with severe pulmonary hypertension. *Gac Med Mex* 2006; 142:19-28.

17. Beaver WL, Wasserman K, Whipp BJ. A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol* 1986; 60:2020-2027.

18. Wensel R, Opitz CF, Ewert R, Bruch L, Kleber FX. Effects of iloprost inhalation on exercise capacity and ventilatory efficiency in patients with primary pulmonary hypertension. *Circulation* 2000; 101: 2388–2392

19. Davies LC, Francis D, Jurák P, Kára T, Piepoli M, Coats AJ. Reproducibility of methods for assessing baroreflex sensitivity in normal controls and in patients with chronic heart failure. *Clin Sci (Lond)* 1999; 97: 515–522.

20. Heart rate variability: standards of measurement, physiological interpretation and clinical use. Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. *Circulation* 1996; 93:1043-1065.

21. Ponikowski P, Chua TP, Piepoli M, Ondusova D, Webb-Peploe K, Harrington D, Anker SD, Volterrani M, Colombo R, Mazzuero G, Giordano A, Coats AJ. Augmented peripheral chemosensitivity as a potential input to baroreflex impairment and autonomic imbalance in chronic heart failure. *Circulation* 1997; 96: 2586-2594.

22. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Gas exchange detection of exercise-induced right-to-left shunt in patients with primary pulmonary hypertension. *Circulation* 2002; 105:54-60.

23. Wensel R, Opitz CF, Anker SD, Winkler J, Höffken G, Kleber FX, Sharma R,

Hummel M, Hetzer R, Ewert R. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002; 106:319-324.

24. Frenneaux MP. Autonomic changes in patients with heart failure and in post-myocardial infarction patients. *Heart* 2004; 90;1248-1255.

25. Casadei B, Cochrane S, Johnston J, Conway J, Sleight P. Pitfalls in the interpretation of spectral analysis of the heart rate variability during exercise in humans. *Acta Physiol Scand* 1995; 153:125-131.

26. Sleight P, La Rovere MT, Mortara A, Pinna G, Maestri R, Leuzzi S, Bianchini B, Tavazzi L, Bernardi L. Physiology and pathophysiology of heart rate and blood pressure variability in humans: is power spectral analysis largely an index of baroreflex gain? *Clin Sci (Lond)* 1995; 88:103-109.

27. Davos CH, Francis DP, Leenarts MF, Yap SC, Li W, Davlouros PA, Wensel R, Coats AJ, Piepoli M, Sreeram N, Gatzoulis MA. Global impairment of cardiac autonomic nervous activity late after the Fontan operation. *Circulation* 2003; 108:II180-85.

28. Davos CH, Davlouros PA, Wensel R, Francis D, Davies LC, Kilner PJ, Coats AJ, Piepoli M, Gatzoulis MA.Global impairment of cardiac autonomic nervous activity late after repair of tetralogy of Fallot. *Circulation* 2002; 106:I69-75.

29. Piepoli M, Clark AL, Volterrani M, , Adamopoulos S, Sleight P, Coats AJ. Contribution of muscle afferents to the hemodynamic, autonomic, and ventilatory responses to exercise in patients with chronic heart failure: effects of physical training. *Circulation* 1996; 93:940-52.

30 Swedberg K, Cleland J, Dargie H, Drexler H, Follath F, Komajda M, Tavazzi L, Smiseth OA, Gavazzi A, Haverich A, Hoes A, Jaarsma T, Korewicki J, Lévy S, Linde C, Lopez-Sendon JL, Nieminen MS, Piérard L, Remme WJ; Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology.. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J* 2005; 26:1115-1140.

31. Sun XG, Hansen JE, Oudiz RJ, Wasserman K. Exercise pathophysiology in patients with primary pulmonary hypertension. *Circulation* 2001; 104:429-35.

32. D'Alonzo GE, Gianotti LA, Pohil RL, Reagle RR, DuRee SL, Fuentes F, Dantzker DR. Comparison of progressive exercise performance of normal subjects and patients with primary pulmonary hypertension. *Chest* 1987; 92:57-62.

33. MacGregor AJ, Canavan R, Knight C, Denton CP, Davar J, Coghlan J, Black CM . Pulmonary hypertension in systemic sclerosis: risk factors for progression and consequences for survival. *Rheumatology* (Oxford) 40:453-459.

34. Gläser S, Lodziewski S, Koch B, Opitz CF, Völzke H, Ewert R.. Influence of the incremental step size in work rate on exercise response and gas exchange in patients with pulmonary hypertension. *BMC Pulm Med* 8:3.

35. Liu JL, Pliquett RU, Brewer E, Cornish KG, Shen YT, Zucker IH. Chronic endothelin-1 blockade reduces sympathetic nerve activity in rabbits with heart failure. *Am J Physiol Regul Integr Comp Physiol* 2001; 280:R1906-13.

36. Krum H, Bigger JT Jr, Goldsmith RL, Packer M. Effect of long-term digoxin therapy on autonomic function in patients with chronic heart failure. *J Am Coll Cardiol* 1995; 25:289-94.

37. Panzenbeck MJ, Tan W, Hajdu MA, Zucker IH. Intracoronary infusion of prostaglandin I2 attenuates arterial baroreflex control of heart rate in conscious dogs. *Circ Res* 1988; 63:860-8.

Figure legends:

Figure 1: High-frequency (a), low-frequency (b) and very low-frequency (c) spectral power in patients with PAH vs. controls, * $p<0.01$.

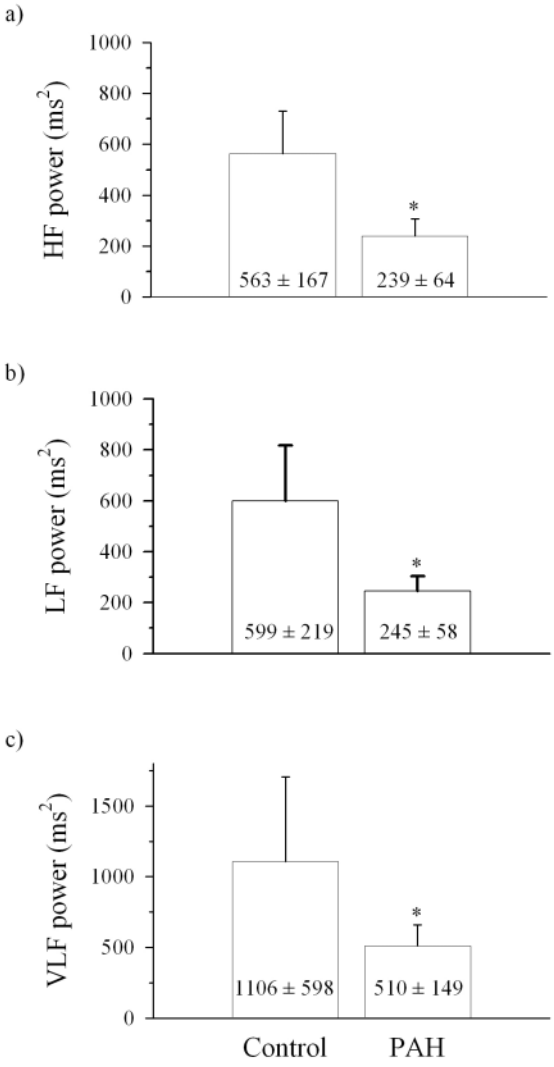

a)
HF power (ms^2)
1000
800
600
400
200
0
563 ± 167
239 ± 64
*
b)
LF power (ms^2)
1000
800
600
400
200
0
599 ± 219
245 ± 58
*
c)
VLF power (ms^2)
1500
1000
500
0
1106 ± 598
510 ± 149
*
Control
PAH

Figure 2: Baroreflex sensitivity as assessed by controlled breathing (a), sequence method (b) and α-index (c), in patients with PAH vs. controls, * $p<0.001$.

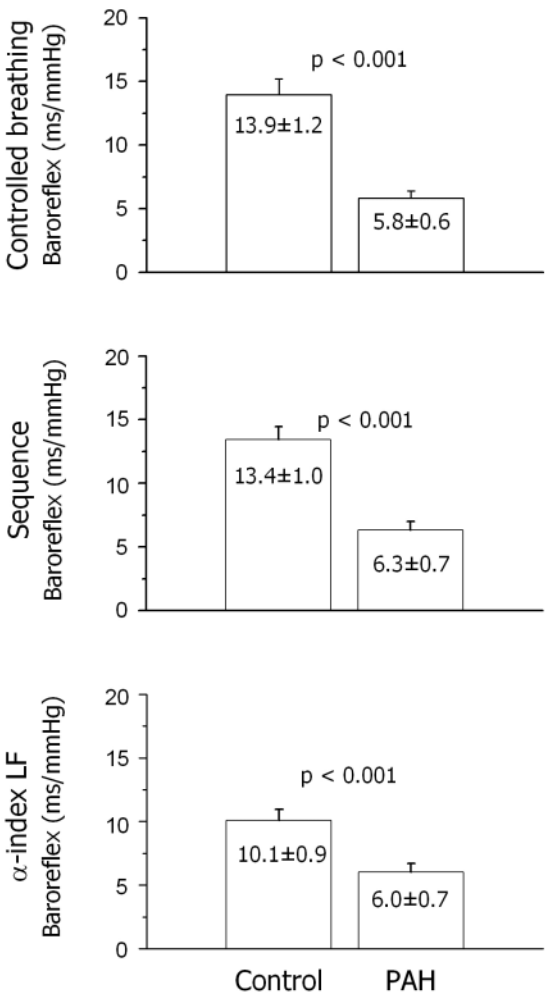
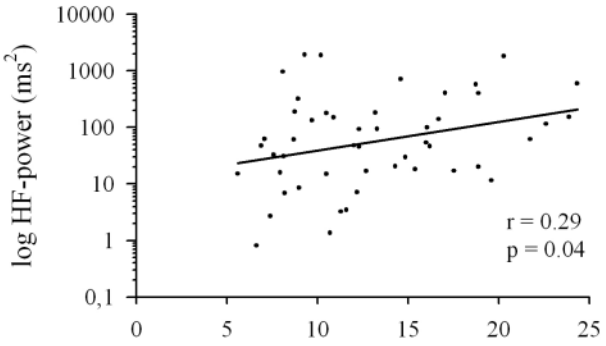

Controlled breathing
Baroreflex (ms/mmHg)
20
15
10
5
0
p < 0.001
13.9±1.2
5.8±0.6
Sequence
Baroreflex (ms/mmHg)
20
15
10
5
0
p < 0.001
13.4±1.0
6.3±0.7
α-index LF
Baroreflex (ms/mmHg)
20
15
10
5
0
p < 0.001
10.1±0.9
6.0±0.7
Control
PAH

Figure 3: Relationship between spectral power in a) high frequency and b) low frequency band and peak oxygen uptake.

a)


10000
1000
100
10
1
0,1
log HF-power (ms^2)
r = 0.29
p = 0.04
0
5
10
15
20
25

b)

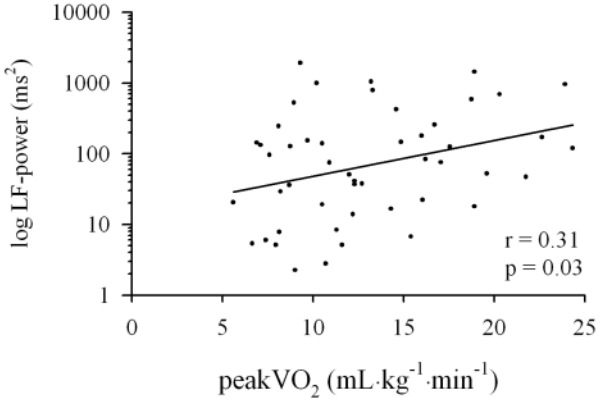
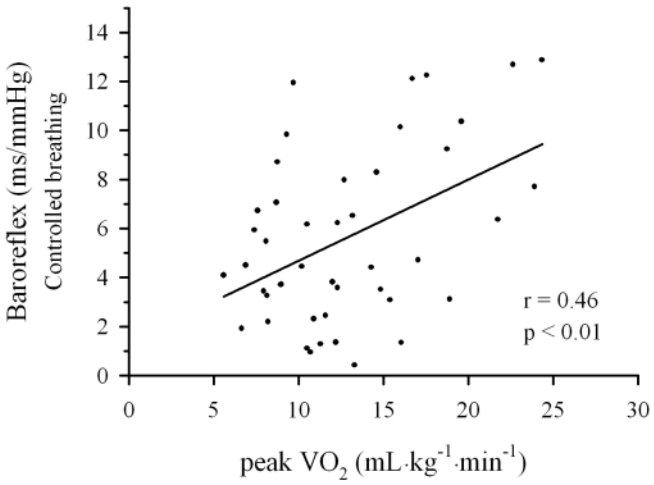

10000
1000
100
10
1
log LF-power (ms^2)
r = 0.31
p = 0.03
0
5
10
15
20
25
peakVO$_2$ (mL·kg^{-1}·min^{-1})

Figure 4: Relationship between baroreflex sensitivity as measured by the controlled breathing method and peak oxygen uptake.


Baroreflex (ms/mmHg)
Controlled breathing
14
12
10
8
6
4
2
0
0
5
10
15
20
25
30
r = 0.46
p < 0.01
peak VO2 (mL·kg-1·min-1)