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Effects of oxygen on autonomic nervous system dysfunction in patients with chronic obstructive pulmonary disease

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ABSTRACT: Chronic hypoxaemia can play a pathological role in abnormalities of the autonomic nervous system (ANS). In patients with chronic obstructive pulmonary disease (COPD), chronic hypoxaemia is associated with increased mortality and only long-term oxygen therapy is able to improve their survival. Normoxaemic COPD patients have been shown to suffer from abnormalities in ANS function. The aims of this study were to evaluate ANS function in COPD patients with chronic hypercapnic respiratory insufficiency and to test whether oxygen supplementation could reverse any ANS dysfunction.

Eleven stable COPD patients with chronic hypercapnic respiratory insufficiency underwent evaluation of ANS by analysis of variability in cardiac frequency at rest and during both vagal (controlled breathing) and sympathetic (tilting) stimuli breathing with and without oxygen supplementation. Thirteen male, healthy, nonsmoking volunteers served as controls.

Evaluation of ANS in COPD patients during hypoxic conditions showed alterations both at rest and in response to vagal and sympathetic stimuli. Oxygen supply reversed hypoxaemia without significant changes in arterial carbon dioxide tension and, therefore, ANS alterations were corrected during sympathetic stimulus only. Breathing room air and oxygen, the resting low-frequency (LF) powers were 45±15 and 148±55 $ms^2 \cdot Hz^{-1}$, respectively, and controlled breathing LF were 107±41 and 141±113 $ms^2 \cdot Hz^{-1}$, respectively.

In stable patients with chronic obstructive pulmonary disease with chronic respiratory insufficiency, hypoxaemia is associated with derangements in the autonomic nervous system which may be partially reversed by oxygen administration.

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It has been demonstrated that chronic hypoxaemia can have a pathological role in diabetic peripheral neuropathy, which is associated with derangement in the autonomic nervous system (ANS) [1]. In patients with chronic obstructive pulmonary disease (COPD), chronic hypoxaemia is associated with increased mortality and only long-term oxygen therapy (LTOT) is able to improve the survival of these patients [2, 3]. Normoxaemic COPD patients have been shown to suffer from abnormalities in ANS function [4, 5]. Hypoxaemic COPD patients were found to show a subclinical autonomic neuropathy which did correlate with the severity of hypoxaemia and was not reversed by correction of hypoxaemia for 1 h [6].

Analysis of the variability in cardiac frequency (heart rate variability (HRV)) has been proposed as a useful tool in assessing ANS function [7]. Decreased HRV is an early and sensitive marker of diabetic neuropathy [8] and is a powerful index of poor outcome after myocardial infarction [9, 10]. The aim of this study was therefore to use this method to evaluate ANS function in stable COPD patients with chronic hypercapnic respiratory insufficiency and to test whether oxygen supplementation could reverse any ANS dysfunction.

Subjects and methods

Patients gave their informed consent to participate in the study, which was approved by the Ethical Committee of Salvatore Maugeri Foundation and was conducted according to the Declaration of Helsinki.

Patients

Eleven consecutive patients in a stable condition with chronic hypercapnia were recruited during the period between July 1, 1996 and December 31, 1996. COPD was defined according to American Thoracic Society (ATS) criteria [11]. In addition, arterial oxygen tension (P_{a,O_2}) and carbon dioxide tension (P_{a,CO_2}) had to be <8 kPa (60 mmHg) and >6 kPa (45 mmHg), respectively, during spontaneous breathing of room air at the time of the study. The demographic, anthropometric and functional characteristics of patients are shown in table 1. Patients with overt cardiovascular or musculoskeletal disease, other organ failure, diabetes (by blood glucose level assessment), neurological problems, cancer or inability to cooperate were

Table 1. – Demographic, anthropometric and functional characteristics of patients in the study

Patients n	11
Sex M/F	8/3
Age yrs	65±8
Weight kg	65±14
Height cm	164±8
FVC % pred	42±13
FEV_1 % pred	28±9
FEV_1/FVC %	53±12
FRC % pred	144±45
P_{a,O_2} kPa	7.6±0.7
P_{a,CO_2} kPa	7.0±0.9
pH	7.38±0.03

Data are mean±SD. M: male; F: female; FVC: forced vital capacity; FEV_1: forced expiratory volume in one second; FRC: functional residual capacity; P_{a,O_2}: arterial oxygen tension; P_{a,CO_2}: arterial carbon dioxide tension.

excluded from the study. All of the patients were on LTOT, whereas no patient was on long-term home mech-anical ventilation. All of the patients were in sinus rhythm and none had any history of acute myocardial infarction or had undergone cardiac surgery. Subjects with >10·min^{-1} supraventricular and/or ventricular extrasystoles at Holter monitoring were excluded. All patients were receiving inhaled bronchodilators as regular treatment. None of the subjects were taking oral or inhaled steroids, β-blockers, long-acting theophylline or long-acting β_2-agonists. Patients taking medications likely to interfere with the tests, such as vasodilators and angiotensin-converting enzyme inhibitors, were also excluded. No change in medical and oxygen therapy was made during the week preceding the study. All medications were discontinued for 24 h before the study session.

Thirteen male, healthy, nonsmoking volunteers (mean age 51±7 yrs) without significant respiratory or cardiac disorders or other pathology that could affect cardiac frequency served as controls.

Measurements

Pulmonary function tests. Lung volumes and forced vital capacity (FVC) were measured by means of a constant volume body plethysmograph (CAD/NET System, Medical Graphic Corp., St. Paul, MN, USA). The predicted values according to QUANJER [12] were used.

Arterial blood gases. Arterial blood was sampled from the radial artery with the patients in the supine position. P_{a,O_2}, P_{a,CO_2} and pH were measured by means of an automated analyser (ABL 300; Radiometer, Copenhagen, Denmark).

Assessment of variability in cardiac frequency. A complete description of the method to assess HRV can be found elsewhere and goes beyond the purposes of this study [13–15]. In brief, cardiac and respiratory frequency were monitored by means of a pneumograph (Kolormon module 7271; Kontron Instruments, Watford, UK) with three surface electrodes placed on the chest and on the upper abdomen. The electrocardiographic (ECG) and respiratory signals were recorded through an ECG respiratory monitor (Kolormon module 7271). A dedicated computer program acquired the ECG signal sampled at a frequency of 1,000 Hz throughout each ECG R-wave.

Data analysis. The recorded time series were analysed to obtain variability indices in both the time and frequency domains following the method described previously [7, 16–18].

Time domain analysis. The following time domain measures of HRV were evaluated: the mean of all R–R intervals for each period (resting, controlled breathing, passive orthostatism, see below) and the standard deviation of all R–R intervals (SD_{RR}), an index of total HRV.

Frequency domain analysis. The measurements of HRV in the frequency domain were computed by an autoregressive spectral technique [9, 13]. This technique calculates the model for the data generation mechanism by a least-square minimization of the prediction error. Such a model allows the entire spectrum to be divided into single spectral components, one for each degree of freedom of the model itself. The optimal order of autoregressive model identification was chosen by minimization of the Akaike Information Criteria figure of merit [9, 13]. This provides the best spectral resolution allowing spectral decomposition with automatic identification of the low-frequency (LF) and high-frequency (HF) components [19–21]. The HF component has been used as a marker of vagal activity, whereas both vagal and sympathetic outflows modulate LF. Thus, the LF/HF ratio is considered as a marker of sympathovagal balance [22]. The LF/HF ratio increases during sympathetic stimulation and decreases during vagal stimulation.

Study protocol

Holter monitoring was performed the day before the study. Patients were examined in the morning, after a light meal, in a room with constant temperature and humidity. The subjects were trained to breathe in synchrony with a metronome at 15 breaths·min^{-1} (0.25 Hz) to ensure that respiratory-linked variations in cardiac frequency did not overlap with LF fluctuations in cardiac frequency (<0.12 Hz) due to nonrespiratory causes.

Assessment of HRV was performed according to a randomly assigned AB–BA scheme, breathing either room air or oxygen with an inspiratory oxygen fraction (F_{I,O_2}) able to maintain an arterial oxygen saturation (S_{a,O_2}) >93%. Studies in room air were performed at least 1 h after discontinuation of oxygen. In both conditions (breathing with and without oxygen), after adaptation to the environment and at least 30 min after arterial puncture for blood gases, the study protocol involved three periods, each lasting for 600 cardiac cycles: 1) resting, with the subject quietly recumbent; 2) controlled breathing at 15 breaths·min^{-1}, to enhance the vagal-mediated respiratory component of HRV; and 3) passive orthostatism, produced by a head-up tilt manoeuvre to upright position (80°) (tilting) as a sympathetic stimulus. S_{a,O_2} was monitored continuously by pulse oximetry (Oxicap Monitor, Ohmeda, Louisville, CO, USA) during the whole procedure.

Statistical analysis

All data are expressed either as mean±SEM or as mean±SD. Shapiro–Wilk′s W-Stat, Kurtosis and Skewness were applied to test the normality of distribution of each variable. Where the test of normality failed, appropriate transformations were used. Two-way analysis of variance (ANOVA) for repeated measures was performed to compare controls *versus* COPD breathing room air and controls *versus* COPD breathing oxygen. ANOVA for repeated measures was used to assess changes before and after oxygen supply in COPD patients. Correction for degrees of freedom in the sample effect of repeated measures was calculated by Greenhouse–Geisser when appropriate (significant value in interaction between groups effect and condition effect). t-Tests with Bonferroni′s correction were applied to explain the contrast relation. Paired (arterial blood gases with and without oxygen in COPD) and unpaired comparisons were performed by t-test. A p-value <0.05 was regarded as statistically significant throughout the study.

Results

All patients suffered from severe airway obstruction and hyperinflation. Arterial blood gas analysis showed hypoxaemia and hypercapnia (table 1). Oxygen administration resulted in the correction of hypoxaemia without significant changes in P_{a,CO_2} (from 7.6±0.7 to 10.7±1.5 and from 7.0±0.9 to 6.9±0.9 kPa for P_{a,O_2} and P_{a,CO_2}, respectively). During oxygen supplementation the F_{I,O_2} needed to obtain the target S_{a,O_2} remained unchanged throughout all conditions.

Data of HRV in COPD patients during air breathing and oxygen supply and in controls respectively are reported in figure 1 and tables 2 and 3.

Healthy subjects versus patients with COPD breathing room air

All parameters of ANS in COPD patients were lower than in controls in all conditions assessed (fig. 1). As also shown in tables 2 and 3, the LF/HF ratio did not change significantly during the different conditions in COPD, whereas healthy subjects showed the expected physiological changes.

COPD patients breathing room air showed different ANS behaviour from controls during parasympathetic and sympathetic stimulation. Control subjects had a normal modulation of LF and HF, as demonstrated by the expected changes in HF and LF during controlled breathing (a parasympathetic stimulus) and during tilting (a sympathetic stimulus) [18]. In contrast to controls, patients failed to exhibit any change in either LF or HF components following sympathetic and parasympathetic stimulation, indicating an abnormal modulation of ANS (fig. 1c and d).

During oxygen supply

Administration of oxygen to COPD patients resulted in an increase in resting mean R–R to such an extent that the

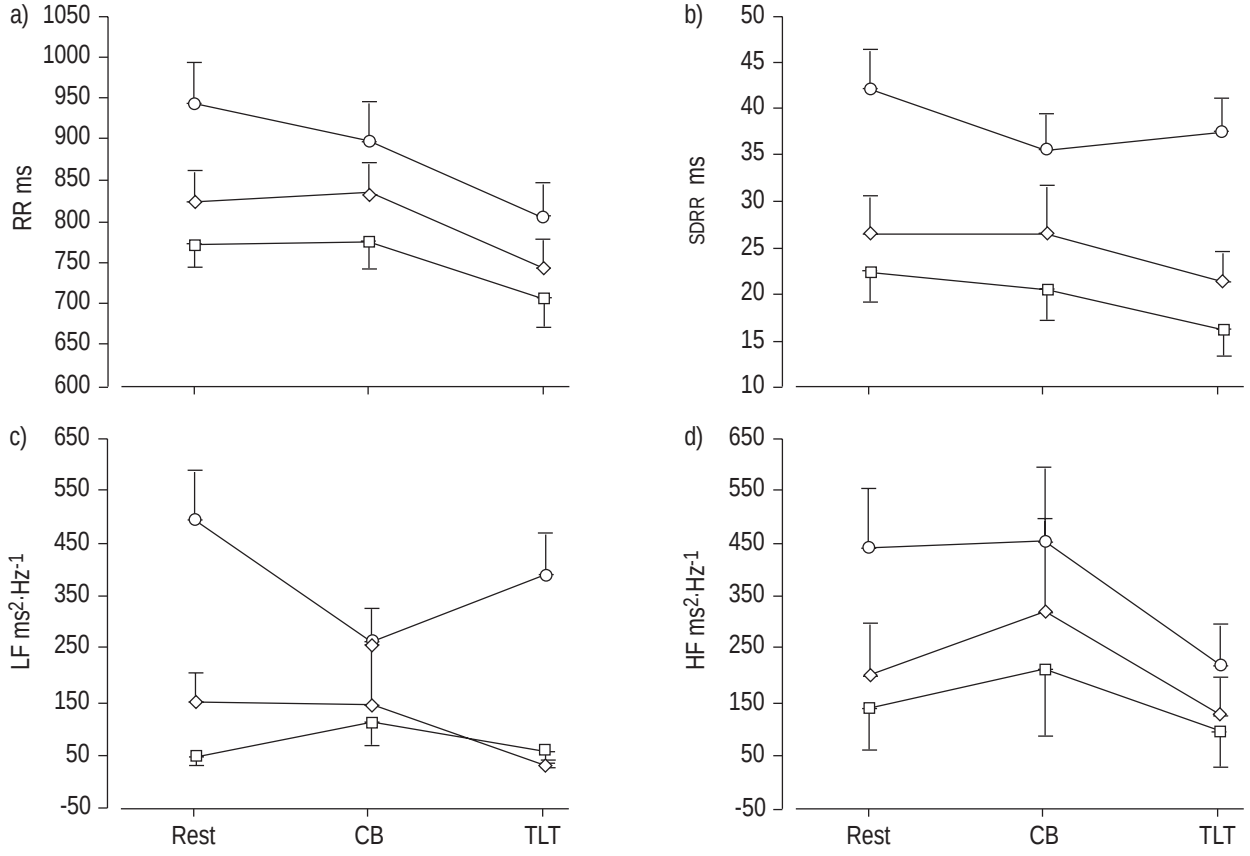

Fig. 1. – Heart rate variability (mean±SEM) in controls (○), in patients with chronic obstructive pulmonary disease breathing air (□) or oxygen (◇), at rest, during controlled breathing (CB) and during tilting (TLT). a) Mean of R–R interval (RR); b) mean standard deviation of R–R interval (SD_{RR}); c) low frequency (LF) spectra power; and d) high frequency (HF) spectra power.

Table 2. – Heart rate variability in controls and patients

	Controls	COPD R-A	COPD O_2-B
P_{a,O_2} kPa		7.6±0.2	10.7±0.4
RR ms			
Rest	944±48	771±27‡	823±35
CB	897±46	774±31‡	833±36
TLT	804±40	704±32	743±32
SD_{RR} ms			
Rest	42±4	22±3	26±12
CB	35±3	20±3	26±5
TLT	37±3	15±3	21±3
LF $ms^2 \cdot Hz^{-1}$			
Rest	454±98	45±15‡	148±55†
CB	258±65	107±41	141±113
TLT	357±82	53±21‡	25±10
HF $ms^2 \cdot Hz^{-1}$			
Rest	442±113	138±77	199±102
CB	455±138	209±122	323±180
TLT	218±77	96±65	120±82
LF/HF			
Rest	2.2±0.8	0.8±0.2	2.2±1.0
CB	1.4±0.6	2.8±1.0	0.9±0.2
TLT	9.2±3.0	4.0±2.0	1.5±0.7

Data are presented as mean±SEM; COPD R-A: patients with chronic obstructive pulmonary disease (COPD); COPD O_2-B: COPD patients breathing oxygen; P_{a,O_2}: arterial oxygen tension; RR: mean of R–R interval; SD_{RR}: mean standard deviation of R–R interval; LF: low-frequency spectra power; HF: high-frequency spectra power; CB: controlled breathing; TLT: tilting. †: $p<0.05$ *versus* O_2-B; ‡: $p<0.05$ *versus* controls (ANOVA; t-test).

Table 3. – Statistical analysis of heart rate variability in controls and patients

	COPD R-A *versus* O_2-B	Control *versus* COPD in R-A	Control *versus* COPD in O_2-B
RR ms			
GC		$F_{2,\ 44}3.6$**	
C	$F_{2,\ 20}26.6$**		$F_{2,\ 44}35.8$**
G	$F_{1,\ 10}22.1$**		
SD_{RR} ms			
GC			
C	$F_{2,\ 20}5.9$**	$F_{2,\ 44}6.8$**	$F_{2,\ 44}4.1$**
G	$F_{1,\ 10}12.4$**	$F_{1,\ 22}16.6$**	$F_{1,\ 22}7.0$**
LF $ms^2 \cdot Hz^{-1}$			
GC	$F_{2,\ 20}4.7$*	$F_{2,\ 44}3.4$**	
C			
G			$F_{1,\ 22}12.4$**
HF $ms^2 \cdot Hz^{-1}$			
GC			
C	$F_{2,\ 20}8.1$**	$F_{2,\ 44}16.9$**	$F_{2,\ 44}16.9$**
G		$F_{1,\ 22}6.2$**	
LF/HF			
GC			$F_{2,\ 44}14.3$**
C		$F_{2,\ 44}9.9$**	
G			

Data are presented as analysis of variance (ANOVA) results. COPD: chronic obstructive pulmonary disease patients breathing room air (R-A) or breathing oxygen (O_2-B); GC: interaction between group and condition effect; C: condition effect; G: group effect. Other definitions as in table 2. *: $p<0.05$; **: $p<0.01$ (ANOVA).

difference from controls was not significant (fig. 1a). During oxygen supply resting SD_{RR} was significantly higher than when breathing air (ANOVA; $p<0.01$), but still significantly lower than that in the control group (fig. 1b). During O_2 supply the resting LF of COPD patients was significantly higher than when breathing air (fig. 1c).

In comparison to breathing room air, patients on oxygen still failed to exhibit any change in LF under any stimulation (fig. 1c), whereas HF showed a modulation similar to controls (fig. 1d). Taken together, these results indicate that oxygen administration only partially corrects ANS dysfunction.

Discussion

This study shows that chronically hypoxaemic COPD patients may suffer from abnormal behaviour of the ANS as assessed by a significant reduction in HRV and a markedly abnormal response to vagal and sympathetic stimuli such as controlled breathing and tilting, respectively. This study also shows that correction of hypoxaemia partially reverses these abnormalities.

Although STEWART *et al.* [6] also studied cardiovascular autonomic nerve function in patients with hypoxaemic COPD; to the authors' knowledge this is the first study evaluating the effects of reversal of hypoxaemia on ANS by means of HRV assessment. Recently, STEIN *et al.* [5] showed that PiZ α1-antitrypsin deficiency COPD is associated with abnormal cardiac autonomic modulation. In that study indices of HRV appeared to reflect the severity of diseases. It has been shown previously that stable COPD patients without chronic respiratory insufficiency exhibit a quite normal HRV in the resting condition, whereas their response to vagal and sympathetic stimuli is abnormal [4]. In contrast to these patients, this study shows that more severe COPD patients with chronic respiratory insufficiency also have ANS abnormalities in the resting condition. These differences may be ascribed at least in part to hypoxaemia. Indeed, oxygen supplementation was associated with resting HRV similar to control subjects and with partial reversal of the abnormalities in response to vagal stimulus (controlled breathing). In contrast, abnormalities in response to sympathetic stimulus (tilting) remained unchanged. A hypothetical effect of hypercapnia in response to a vagal stimulus may be excluded on the basis of the lack of change in P_{a,CO_2} during oxygen supply. However, an effect of hypercapnia on the abnormal response to the sympathetic stimulus cannot be ruled out as neither P_{a,CO_2} nor the response to sympathetic stimuli changed during O_2 supplementation.

The present results only confirm in part those of STEWART *et al.* [6], who found a different level of autonomic dysfunction in up to 82% of hypoxaemic COPD patients. In a subgroup of hypoxaemic and hypercapnic COPD patients they also found an alteration in systolic blood pressure response to standing, which is considered a sympathetic stimulus. In contrast to the present study these authors found that correction of hypoxaemia had no effect on autonomic function. This difference may be explained on the basis of the method used to assess ANS. STEWART *et al.* [6] evaluated cardiac frequency and blood pressure response to a series of stimuli, through short recordings of R–R intervals. In the present study ANS was evaluated by

means of the HRV method, both in the time and frequency domain in different conditions. This method has been recommended to assess the role of the ANS fluctuations in healthy individuals and in patients with various cardiovascular and noncardiovascular diseases [7]. The method used here, involving a longer recording of cardiac frequency (at least 600 beats) may well have resulted in a higher sensitivity than that used by STEWART *et al.* [6].

The lack of correction in the LF component in response to a sympathetic stimulus deserves further discussion. In particular, the abnormal behaviour of LF could be explained as the loss of the autonomic cardiac frequency modulation. When sympathetic output is maximal, as during tilting, modulation of cardiac frequency is not possible. The sinus node is maximally stimulated so that the cardiac frequency is fixed and no longer fluctuates in the LF or HF band to any appreciable extent. The reduced LF component was also found in patients with chronic heart failure [23–25]. MORTARA *et al.* [26], in a series of 30 patients with advanced stage heart failure, observed that patients with an undetectable LF component were more severely affected, with more depressed left ventricular function and a higher degree of sympathetic excitation, as reflected by higher plasma concentrations of noradrenaline. Whether an undetectable or a reduced LF component may also be associated with worse prognosis in COPD patients has not yet been demonstrated.

Chronic hypoxaemia is associated with reduced survival in COPD patients, which may be reversed by LTOT [2, 3]. Hypoxia is considered to be related to peripheral neuropathy in diseases such as diabetes, with a high incidence of sudden death [27, 28]. WATSON *et al.* [29] showed that patients with musculoskeletal chest wall abnormalities and nocturnal hypoxia have severe autonomic dysfunction (marked reduction in SD_{RR}) compared with patients with similar chest wall abnormalities without hypoxia. Decreased HRV with altered cardiac autonomic modulation is associated with an increased risk of cardiac events in clinically disease-free subjects, even after adjusting for known risk factors [30]. Reduced HRV is observed after acute myocardial infarction [9, 10] and it has been shown to correlate well with left ventricular dysfunction and poor prognosis. The patients in the present study were older than 50 yrs and although carefully checked, at least hypothetically, subclinical concomitant cardiovascular diseases cannot be ruled out. This might explain the partial reversal of ANS abnormalities with oxygen. It cannot be excluded that reduced survival in hypoxic COPD may be contributed to by ANS dysfunction. Therefore, the well-accepted favourable effect on survival of LTOT in these patients might, at least in part, be ascribed to its effect on ANS. The results show a reversal, although only partial, in ANS alterations in hypoxaemic COPD patients; this may indicate the need to perform LTOT continuously to avoid even short periods of ANS dysfunction. Whether short periods of ANS alterations may significantly affect survival remains to be elucidated.

In conclusion, patients with chronic obstructive pulmonary disease with hypoxaemia may suffer from an abnormal autonomic nervous system, as assessed by reduced variability in cardiac frequency and abnormal responses to vagal and sympathetic stimuli, which may be partially corrected by oxygen-induced reversal of hypoxaemia.

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