Decreased Heart Rate Variability in Patients With Chronic Obstructive Pulmonary Disease

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Decreased Heart Rate Variability in Patients With Chronic Obstructive Pulmonary Disease*

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To evaluate possible autonomic nervous system (ANS) dysfunction in patients with chronic obstructive pulmonary disease (COPD) in the absence of any hypoxic neuronal damage, we studied 31 patients with COPD patients aged 31 to 68 years (55 ± 10) and 32 age-matched healthy subjects (control). Respiratory function in the patients was as follows: FEV_1=52 ± 8 percent; PaO_2= 71 ± 14 mm Hg; and $PaCO_2$=40 ± 10 mm Hg. The ANS was assessed by heart rate variability (HRV) in the time domain (SD of mean RR interval) and frequency domain (autoregressive spectral analysis recognizing low [LF] and high [HF] frequency components, vagal and sympathetic related, respectively). Patients and controls were evaluated at rest and during vagal (controlled breathing [CB]) and sympathetic (passive head-up tilt) maneuvers. Patients with COPD showed a depressed global HRV (rest SD=34 ± 20 ms vs 45 ± 15 ms, p<0.05; tilt SD=28 ± 14 ms vs 38 ± 13, p<0.01) with a predominant respiratory drive (rest HF=44 ± 28 vs 28 ± 18, p<0.05; tilt HF 42 ± 28 vs 16 ± 12, p<0.01) as compared with normal subjects. In the control group, vagal and sympathetic responses were in opposite directions following a stimulus, whereas there was no significant HRV response in the COPD group. We conclude that patients with COPD have abnormalities of ANS function, with in particular a depressed HRV response to sympathetic and vagal stimuli.

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ANS=autonomic nervous system; CB=controlled breathing; HF=high frequency; HRV=heart rate variability; LF=low frequency; nu=normalized unit

Key words: autonomic nervous system; COPD; heart rate variability; power spectral analysis

Previous studies have established that modulation of human airway tone is mediated through parasympathetic cholinergic,[1,2] sympathetic adrenergic, and nonadrenergic[2] effects as well as by the humoral system (vasoactive intestinal peptide and substance P).[3] Abnormal autonomic control of cardiopulmonary function may make an important contribution to the pathophysiology of patients with chronic obstructive pulmonary disease (COPD). In addition, compared with normal subjects, patients with COPD show an increased airway resistance even in the absence of clinically evident respiratory insufficiency. This could cause the work of breathing to increase, which in turn could affect autonomic nervous function even in the absence of any hypoxic neural damage. The quantification of the balance of parasympathetic and sympathetic nervous system activity may, therefore, be important in understanding the pathophysiology of COPD and might be useful clinically in the treatment of patients with COPD. Spontaneous fluctuations of heart rate reflect the interaction between the perturbations of the cardiopulmonary system and the response of its regulatory systems. The heart rate variability (HRV) analysis, using advanced computers, is a useful tool in assessing the autonomic neurovegetative function. Decreased HRV is an early and sensitive marker of diabetic neuropathy[4] and is a powerful index of poor outcome after myocardial infarction.[5-7]

Since 1970, HRV spectral analysis has been proposed as a noninvasive tool for the quantification of spontaneous HRV in normal humans.[8] The variability of the RR interval can be analyzed by autoregressive spectral analysis to give a spectrum of variability frequencies. The power spectral analysis allows the determination of two major components, one reflecting respiratory sinus arrhythmia (0.2 to 0.3 Hz), and the second compounding the low-frequency (LF) fluctuations (0.03 to 0.15 Hz) that reflect the modulation on the arterial blood pressure and peripheral circulation.[9-13] In the last few years, several studies[14-16] have shown that LF fluctuations in heart rate (around 0.1 Hz) are jointly mediated by the

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sympathetic and parasympathetic systems whereas the higher-frequency (HF) fluctuations are mediated solely by the parasympathetic system. In particular, LF fluctuations are increased by standing, and several authors[14-17] have shown a very strong sympathetic input to LF variability, related to changes of posture and blood pressure.[9,10,14] Moreover, power spectrum analysis has provided information about cross-correlation between respiratory patterns and HF components of HRV,[9,11,12] so showing the respiratory drive to be an important component of HF HRV.

Aim of the Study

The aim of this study was to evaluate by HRV analysis the presence of autonomic dysfunction in patients with COPD and to determine whether the pattern of HR variability in this population is different from the normal population.

METHODS

Study Population

Informed consent was obtained from 31 male inpatients with a history of COPD, as defined by the American Thoracic Society,[18] and 32 aged-matched control subjects. The patients were between 31 and 68 years of age (mean=55 ± 10), normoxemic (mean PaO_2=70.85 ± 13.93 mm Hg) and with a forced expiratory volume in 1 s (FEV_1) of less then 65 percent of the predicted value (mean=52 ± 8.3 percent). Exclusion criteria were as follows: coronary artery disease; hypertension; encephalopathy; and diabetic neuropathy. Patients taking medications likely to interfere with the tests, such as vasodilators, angiotensin-converting enzyme inhibitors, and antihypertensive agents, were also excluded.

Experimental Procedures

FEV_1 and forced vital capacity (FVC) were recorded on a spirometer (Ergostar). Arterial blood gases were taken at rest before the autonomic tests and measured using a pH/blood gas analyzer (Radiometer). All patients were taking aminophylline long term in an average dose of 600 mg/d. Treatment with aminophylline, oral β_2-agonists, and steroid medications was discontinued for 24 h before the study. The subjects were trained to breathe in synchrony with a metronome at 15 breaths/min (0.25 Hz), to ensure that respiratory-linked variations in heart rate did not overlap with LF heart rate fluctuation (below 0.12 Hz) from other sources. The patients were studied in the morning, after a light breakfast, in a room with constant temperature and humidity. Three periods made up the study protocol, after adaptation to the environment: (1) rest period, subject quietly recumbent; (2) controlled breathing, 15 cycles/min, to enhance the vagal-mediated respiratory component of HRV;[9] and (3) passive orthostatism, obtained by head-up tilt maneuver to upright position (80°), as a sympathetic provocation.[9] Each period lasted 600 heart cycles.

Acquisition of Data

We recorded the electrocardiographic signal (single channel, lead II) and the respiratory signal (chest impedance variability) by an ECG respiratory monitor (Kontron). A computer program acquired the electrocardiographic signal sampled at 1,000 Hz and the respiratory signal sampled at the frequency of the heart rate, *ie*, each electrocardiographic R wave, throughout.

Analysis of Data

Although a wealth of data with clinical and prognostic significance is available in the time domain,[5,19] frequency domain analysis fits better with cyclic phenomena and should characterize the individual specific pattern of neurovegetative balance. Therefore, the collected time series were analyzed to obtain variability indices both in the time domain and in the frequency domain. The detailed method has been published.[20-22] Time domain analysis provides the following: (1) the mean value of RR intervals (RR) for each period (rest, controlled breathing, passive orthostatism; (2) the SD of the RR interval time series, which is an index of total HR-variability;[5,6,23,24] and (3) the coefficient of variance of the RR-intervals (CV)[25] or normalized SD,[23] *ie*, the ratio SD/RR, which could represent the component of HRV independent of heart rate.[23] Heart rate variability analysis in the frequency domain was performed by means of autoregressive spectral techniques,[20,21] which provides the best spectral resolution and enables spectral decomposition with automatic identification of LF and HF components[11,26] (Fig 1, A). The frequency ranges were subdivided into 0.03 to 0.15 Hz (LF) and 0.18 to 0.35 Hz (HF), respectively.[27] High frequency has been used as a marker of vagal activity, while both vagal and sympathetic outflows modulate LF, so that the ratio LF/HF can be considered a marker of sympatho-vagal balance, LF/HF increases during sympathetic and decreases during vagal stimuli.[13] In this article, we have expressed each component as the relative power, *ie*, percent of filtered total spectral power, in normalized units (nu).[9,13] Normalized units are a standardized index of the presence in percentage, of HF and LF in the total spectrum, calculated as follows:

$$\text{nu (percent)} = \frac{\text{Power of LF or HF}}{\text{Total Power - DC Component}}$$

Normalized units are obtained by dividing the power of a given component by the total variance (from which the component centered at 0.00 Hz, DC component, has been subtracted) and multiplying by 100.

Statistical Analysis

Spectral areas and the mean and SD of the RR intervals were compared between patients with COPD and normal subjects with analysis of variance.

Where appropriate after analysis of variance, additional *t* tests with the Bonferroni correction were used to show the specific differences between the phases (basal, control breathing, tilting). A p value of <0.05 was considered significant.

RESULTS

Table 1 shows the mean values and SDs of measured and computed parameters at rest, during controlled breathing, and in passive head-up tilt.

In patients with COPD, the mean RR interval decreased after passive tilt (858 ± 127 ms vs 738 ± 130.76 ms), whereas there were no statistically significant changes during controlled breathing. Although the mean RR was slightly higher in the normal subjects during the whole test, this was not statistically significant. Significant differences between groups were founded only during controlled breathing, when the mean RR interval increased in normal subjects and decreased in patients. Nevertheless, the SD of the RR interval in patients with COPD was

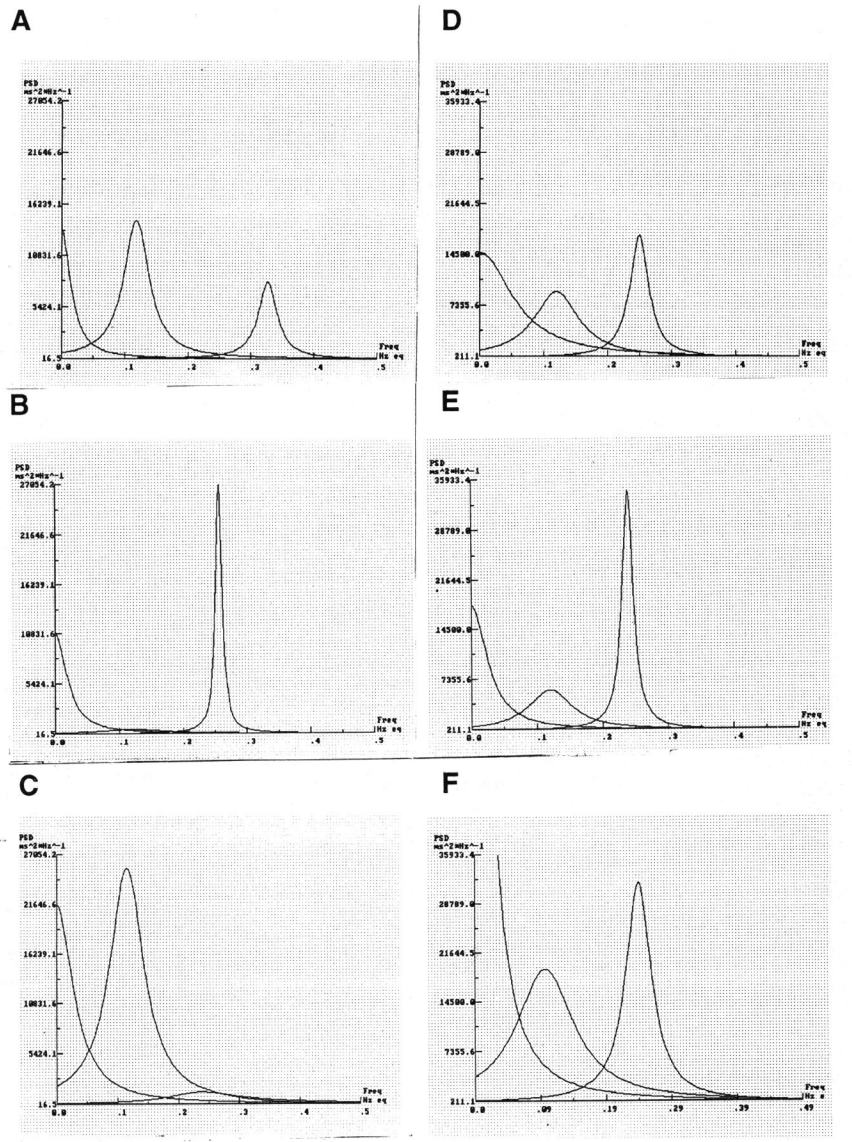

FIGURE 1. *A, B, and C,* HRV power spectra in normal subject at rest, during controlled breathing 16 cycle/min, and during passive orthostatism (tilt). Spectral decomposition allows identification of low frequency (LF) and high frequency (HF) components. PSD = power spectrum density. *D, E, and F,* HRV power spectra of a patient with COPD at rest, during controlled breathing 16 cycle/min, and during passive orthostatism (tilt). In patients with COPD, LF and HF show a markedly abnormal power in response to various stimuli such as controlled breathing or tilting.

significantly lower than in normal subjects at rest (34.40 ± 19.95 vs 44.64 ± 15.20) and after tilting (27.74 ± 14.19 vs 37.64 ± 13.21). The respiratory power spectral analysis shows that there were no differences between the two groups in respiratory rate, at rest, after tilting, and during controlled breathing (Table 2). No significant changes were seen in LF, HF, or in the ratio LF/HF power in patients with COPD after passive orthostatism and controlled breathing, as opposed to normal subjects who showed significant changes (Table 1).

Nevertheless, differences were found between patients and the control group in HF and LF nu. The LF nu in the patients with COPD after tilting was significantly lower ($p<0.05$) than in normal subjects. However, the HF nu showed a much smaller decrease on tilting in the COPD group ($p<0.01$). Thus, after tilting, HF nu was significantly greater in the patients with COPD than in the control group, implying a decreased response to sympathetic stimulation. Figure 1 shows typical spectral analysis of RR interval in a patient with COPD and in a normal subject at rest and during experimental maneuvers.

DISCUSSION

In this study, we have examined the differences in autonomic nervous control of heart rate in 31 patients with COPD compared with an age- and sex-matched control group under standardized conditions, to obtain an index of both static and dynamic neurovegetative balance, *ie*, at rest and during known autonomic stimuli.

The vagus nerve is known to modulate the rate of sinoatrial discharge. The possibility exists that an abnormality in the parasympathetic control of airway caliber may be reflected by a parallel change in the control of heart rate.

We found that in patients with COPD, but with-

Table 1—*Heart Rate Variability in Patients With COPD and the Control Group at Rest and During Stress: Time and Frequency Domain Analysis**

	RR, ms	SD, ms	LF Power	HF Power	LF/HF	LF, nu	HF, nu
COPD							
Rest	858±127	34±45†	301±463	446±1,303	2.6±2.5	51±22	44±27†
Controlled breathing	846±136‡	33±19	274±462	262±382	2.1±3	48±22	39±18
Tilting	739±131§	28±14‡§	183±222	175±462	3.5±4	60±23†	42±28‡
Control							
Rest	914±133	45±15	494±350	208±240	4.5±6	59±17	28±18
Controlled breathing	941±137	40±13	289±202§	284±205	1.3±1§	42±18§	41±18
Tilting	759±103§	38±13§	550±631	117±178§	10±12§	75±18§	16±12§

*RR=RR interval; SD=standard deviation of RR interval; LF-HF power=LF-HF absolute power; LF-HF=LF-HF ratio; LF(nu)-HF(nu)=LF-HF normalized power (using normalized units).
†$p<0.05$, COPD vs control.
‡$p<0.01$, COPD vs control.
§$p<0.01$, tilting or controlled breathing vs rest.

Table 2—*Mean Respiratory Rate During Each Phase in Patients with COPD and in Control Group**

	Rest	Controlled Breathing	Tilt
COPD	13.8±4.2	15±0.6	15.6±3.6
Control	14.8±2.4	15±0	15.8±5.2

*The data are expressed in acts per minute.

out or with only mild evidence of hypoxemia, there was a shift in autonomic nervous system activity that suggests a relative increase in parasympathetic tone.

Our study shows that there were, at rest, significant differences between patients and normal subjects: the increase seen in the HF (nu) in the patient group could suggest an increase in vagal activity, which could in turn explain in part the reduction in FEV_1 and the increase in bronchoconstriction seen in this group. Intrathoracic pressure, increased by breathing against resistance, can affect cardiac function and blood pressure.[28] Large intrathoracic pressure swings, such as those that occur in obstructed breathing, may cause fluctuation in cardiac performance and arterial blood pressure.[28] Thus, both patients with COPD and asthma[29] could have an increase in parasympathetic tone. Nevertheless, the global HRV, represented by the SD of RR interval, is lower in the patients with COPD. The increase in relative vagal activity could be the result of an increase in absolute vagal drive or decrease in sympathetic activity. It seems more correct to say that our patients, with an increase in airways resistance but without hypoxemic neurologic damage, showed a parasympathetic shift, according to the literature.[29,30] It is important, however, to remember that in this study, the patients breathed with a known respiratory rate only during one of the phases. It has been demonstrated that, when breathing frequency is increased, the amplitude of heart rate oscillation decreases.[31-34] In 1981, Hirsch and Bishop[2] confirmed that in respiratory sinus arrhythmia, the amplitude depends on both the depth and frequency of breathing.

The effect of tidal volume on respiratory heart rate variations is small: a 50 percent increase in tidal volume results in only a 15 percent increase in sinus arrhythmia.[35]

Indeed, as the results show (Table 2), the respiratory rate during each phase of the study was the same between the two groups. Thus, any difference between the two groups cannot be attributed to an increase in respiratory rate at rest in the patients with COPD. Abnormally diminished variations in heart rate are generally accepted as proof of the presence of autonomic disorder.[29]

The spectral power at rest in all frequency bands in COPD patients was comparable with normal control subjects, whilst being markedly abnormal in response to various stimuli such as controlled breathing or tilting.

This phenomenon suggests that these patients are less able to respond to sympathetic and parasympathetic stimuli, in comparison with the normal subjects, as Figure 1 shows. In other words, we can speculate that, at rest, these patients are similar to normal subjects. Indeed, there is significant difference between the two groups, but it seems that the COPD patient's control system is working at saturation level, so they could not have the same range of variation of normal people and even opposite stimuli cannot modify their autonomic pattern.

In patients with heart failure, the autonomic system is driven by an exaggerated sympathetic tone.[36,37] Similarly, in our patients with COPD, we have found an altered sympatho-adrenal response to chronic moderate bronchoconstriction. One possible speculation for the lack of RR variability in patients with COPD might be a light constant compensatory sympathetic activity in response to an increase in airways resistance. Larsson et al.[38] suggested that this im-

paired sympatho-adrenal response is not from an alteration of plasma noradrenaline concentrations,[38] however, only patients with acute constriction were studied. Indeed, LF nu in our patients is slightly decreased at rest, although not significantly, as shown in Table 1, but there is no significant response to a massive sympathetic stimulus such as rapid tilting.

Another possibility is that sympathetic outflow response may be normal, but that there could be a block to the action circulating catecholamines, due to receptor down regulation. The down regulation could be due in part to long-term therapy with theophylline or β-agonists and in part to increased circulating endogenous cathecolamines, as discussed earlier.

We have also shown a reduction in the parasympathetic variability. This may be explained by the demonstration that the adrenergic system may have a modulatory influence on cholinergic neurotransmission.[3]

Conclusion

The complexity of the pulmonary effects of the autonomic nervous system is considerable, and our knowledge in this field remains elementary. Our results suggest that in patients with COPD, there is an imbalance in autonomic nervous system activity. This is apparently driven at rest by an increase in vagal activity and through the lack of responsiveness to sympathetic stimulation. This altered balance could contribute to the airways obstruction in COPD.

More studies are needed to increase our understanding of these topics, in particular to estimate in patients with COPD how the alteration in autonomic system correlates with the severity of hypoxemia. Study of autonomic cardiopulmonary control in patients with COPD may have important implications with regard to prognosis in this condition.

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