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Slow breathing reduces sympathoexcitation in chronic obstructive pulmonary disease

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Short title: Slow breathing in COPD

Abstract

Neurohumoral activation has been shown to be present in hypoxic patients with chronic obstructive pulmonary disease (COPD). The aim of this study was to investigate whether there is sympathetic activation in COPD patients in the absence of hypoxia, and whether slow breathing impacts on sympathoexcitation and baroreflex sensitivity.

Efferent muscle sympathetic nerve activity, blood pressure, heart rate and respiratory movements were continuously measured in 15 patients and 15 healthy control subjects. Baroreflex sensitivity was analyzed by autoregressive spectral analysis and the alpha angle method.

At baseline, sympathetic nerve activity was significantly elevated in patients, and baroreflex sensitivity was decreased (5.0 ± 0.6 ms/mmHg vs. 8.9 ± 0.8 ms/mmHg, $p = 0.004$). Breathing at a rate of 6/min caused sympathetic activity to drop significantly in patients (from 61.3 ± 4.6 bursts/100 heartbeats to 53.0 ± 4.3 bursts/100 heartbeats; $p < 0.001$), but not in control subjects (39.2 ± 3.2 bursts/100 heartbeats vs. 37.5 ± 3.3 bursts/100 heartbeats; $p = 0.308$). In both groups, slow breathing significantly enhanced baroreflex sensitivity.

In conclusion, sympathovagal imbalance is present in normoxic COPD patients. The possibility of modifying these changes by slow breathing may help to better understand and influence this systemic disease.

Keywords: chronic obstructive lung disease, sympathetic activity, slow breathing, baroreflex

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide. In COPD, numerous extrapulmonary abnormalities are present. These include systemic inflammation, cachexia and skeletal muscle dysfunction. COPD has thus been called a muscle [1] and a systemic disease [2]. Recent data demonstrate that hypoxemic COPD causes marked neurohumoral activation [3, 4]. Given the established negative connotations of neurohumoral activation in heart failure and other diseases [5], neurohumoral activation in COPD may well have negative consequences, namely on inflammation, cachexia, skeletal muscle dysfunction and cardiovascular disease [4].

Currently, little is known about the cause of the profound sympathetic activation in patients with COPD. Previous data point to a reduced baroreflex sensitivity in COPD patients [4]. This has been shown by spontaneous variations of blood pressure and heart rate [6], the phenylephrine test [7] and the Valsalva manoeuvre [8]. Interestingly, impaired baroreflex sensitivity leads to an increase in sympathetic activity through inhibitory afferents [9].

Lung inflation reflexes mediated by pulmonary vagal afferents may alter the baroreflexes and have been shown to govern the within-breath modulation of muscle sympathetic nerve activity as evaluated by microneurography during normal breathing [10]. In patients with chronic heart failure, sympathetic activation is related to a decrease in tidal volume as well as an attenuated sympatho-inhibitory effect of the lung inflation reflex [11]. Conversely, slow breathing increases arterial baroreflex sensitivity and improved exercise capacity in these patients [9, 12]. It thus seems possible that slow breathing impacts on baroreflex sensitivity and sympathetic outflow in COPD.

Sympathetic activity is accurately quantified by microneurography: Previous investigations have demonstrated that muscle sympathetic nerve activity (MSNA) reflects short-term changes in sympathetic activity, is highly reproducible and correlates closely with cardiac

norepinephrine spillover [13]. We thus aimed to evaluate i) whether sympathetic overactivity is present even in normoxic COPD patients, ii) whether slow breathing impacts on sympathetic tone and baroreflex sensitivity in these patients.

Methods

Subjects

Non-smoking, normoxic individuals aged 30-80 years with stable sinus rhythm and a diagnosis of COPD with a FEV1 $\leq$ 60% predicted who were on medical treatment according to the Global Burden of Disease (GOLD) guideline [14] were eligible for participation in the study. General exclusion criteria were hypercapnia ($PaCO_2$ > 45 mmHg) on arterial blood gas analysis, recent (< 3 months) history of COPD exacerbation, unstable heart disease, polyneuropathy, systemic treatment with sympathomimetic drugs or diagnosis of a disorder known to be accompanied by sympathetic activation.

Healthy non-smoking volunteers were recruited from the general public (advertisements) and matched by sex, age, weight and smoking status to the patients. They did not have any acute or chronic disease and were not on any regular medication.

Patients were asked not to take any diuretic drugs before the measurements were completed. This study was approved by the local ethics committee. Informed written consent was obtained from all patients and control subjects.

Microneurography, respiration and transcutaneous measurement of blood gases

Sympathetic nerve activity was measured using microneurographic recordings of efferent muscle sympathetic nerve activity in the peroneal nerve of the right leg as described previously [15]. Respiratory rate and tidal volume were approximated by calibrated respiratory inductive plethysmography (Respitrace Systems, Ambulatory Monitoring Inc., Ardsley, New York, USA) as previously described [3].

In a set of additional experiments in seven COPD patients, SaO_2 and transcutaneous pCO_2 were assessed using fingertip pulse oxymetry and the Tosca® (Linde Medical Sensors, Basel, Switzerland) device.

Blood pressure, heart rate and baroreflex

Blood pressure was measured automatically and noninvasively with the Portapres device (FMS™, Amsterdam, Netherlands). Heart rate was derived from a continuous electrocardiographic (ECG) recording.

Spontanous Baroreflex sensitivity was measured by spectral analysis using the "alpha-angle" method, as previously described [9, 16]. Briefly, the gain of the arterial baroreflex was obtained by dividing the amount of spontaneous fluctuation in the RR interval by the spontaneous fluctuations of systolic blood pressure at the same frequency. This approach gives results closely correlated to those obtained using the Oxford phenylephrine test and has the advantage of allowing the baroreflexes to be evaluated with no need for external stimulation over a longer time period [17].

Additional detail on the methods used is provided in the online depository of this article.

Protocol

Experiments were conducted in the morning. Subjects were in a supine position with a 30° elevation of the chest during experiments. After obtaining a satisfactory nerve signal, baseline measurements were performed for 20 minutes, after which respiration was regularized by instructions from the investigators. Subjects were instructed to breathe at a respiratory rate of 15/min for 4 minutes, followed by another 4 minutes respiration at 6/min (3 seconds of inspiration, 7 seconds of expiration) [12].

Breathing rates of 6/min were achieved even in patients with severe COPD by a training period with visual feedback.

Data Analysis

Data recording and analysis was performed using the Modular Intensive Care Data Acquisition System (MIDAS) developed by P.H. in cooperation with the Mannheim Biomedical Engineering Laboratories (X.P. Ngyen, MABEL, Institut für Biomedizinische Technik, Hochschule Mannheim, Germany). Sympathetic bursts were quantified manually and independently by two observers (T.R. and F.B.) blinded as to subject and intervention. In our institution, the intraobserver variation in identifying bursts is 5%, and the interobserver variation is 11% [3]. MSNA was computed as bursts/min and bursts/100 heartbeats, both of which yielded similar results. Thus, data are only presented as bursts/100 heart beats. Statistical analyses were carried out with SPSS 12.0.1 (SPSS Inc., Chicago, Illinois, USA). All data in the text and tables are presented as mean ± standard error of the mean (SEM). Statistical significance was accepted at a value of $p \leq 0.05$. Repeated-measures analysis of variance (ANOVA) with time as within-groups factor and the time by treatment interaction as indicator of differential changes in both study groups was used to analyze the effects of slow breathing.

Results

Baseline characteristics

A total of 20 patients and 29 control subjects were included in the study. All patients used long-acting inhaled β_2 agonists, eight added inhaled tiotropium, and three used inhaled glucocorticosteroids. Non-invasive ventilation was not used by any patient. Valid MSNA data could be obtained in 15 COPD patients and 15 healthy control subjects matched in a 1:1 fashion (an exemplary display of the MSNA signal is given in **Figure S1** in the online depository). The baseline characteristics of these participants are summarized in **Table 1**.

The pCO_2 and heart rate was significantly higher in patients when compared to controls. There was no significant difference between the two groups regarding plasma concentrations of epinephrine and norepinephrine.

Under resting conditions, MSNA was significantly higher in patients than in control subjects (59.0 ± 4.5 bursts/100 heartbeats vs. 40.3 ± 2.6 bursts/100 heartbeats, $p < 0.001$; see **Figure 1**).

Owing to difficulties in obtaining a valid blood pressure signal and the presence of ectopic heartbeats in some of the tracings, reliable baroreflex data were only available in 12 COPD patients. These were compared to data from the 12 matched control subjects. At baseline, alpha angle values in controls exceeded those in COPD patients (9.3 ± 1.1 ms/mmHg vs. 5.0 ± 0.6 ms/mmHg, $p = 0.009$; see **Figure 2**).

Regularization of respiratory rate to 15/min and 6/min

Upon regularization of the breathing pattern and standardizing respiratory rate to 15/min, heart rate increased significantly in control subjects (from 69.7 ± 1.7 /min to 71.5 ± 1.7 /min; $p = 0.038$). No significant change in systolic and diastolic blood pressure or sympathetic activity (corrected for heart rate) was observed in either group. At a breathing rate of 15/min, baroreflex sensitivity was significantly higher in control subjects than in COPD patients (7.8 ± 0.9 ms/mmHg vs. 3.3 ± 0.6 ms/mmHg; $p < 0.001$).

When switching from baseline to a respiratory rate of 15/min, minute ventilation increased by 68.3 ± 15.4% in patients and 93.5 ± 25.0% in healthy controls. Upon reduction of respiratory rate from 15/min to 6/min, minute ventilation significantly decreased in both groups (-30.5 ± 4.5% in patients and -32.6 ± 5.9% in controls). Additional experiments in seven COPD patients revealed that SaO_2 increased significantly upon regularizing breathing rate to 15/min (from 94.0 ± 0.9 % to 96.0 ± 0.8%; $p = 0.017$) and 6/min (from 96.0 ± 0.8% to 97.0 ± 0.5%; $p = 0.038$). Transcutaneous pCO_2 decreased from 40.7 ± 0.7 mmHg to 34.2 ± 0.8 mmHg ($p = 0.027$) when breathing rate was set to 15/min. The further decrease to 31.5 ± 1.6 mmHg following the adoption of slow breathing was borderline significant ($p = 0.068$).

Effects of slow breathing on sympathetic activity and baroreflex sensitivity

Slow breathing as opposed to breathing at a respiratory rate of 15/min led to a significant decrease in MSNA in COPD patients (from 61.3 ± 4.6 bursts/100 heartbeats to 53.0 ± 4.3 bursts/100 heartbeats; $p < 0.001$; $n = 15$), but not in healthy controls (39.2 ± 3.2 bursts/100 heartbeats vs. 37.5 ± 3.3 bursts/100 heartbeats; $p = 0.308$; $n = 15$; see **Figure 3**). Repeated-measures analysis of variance (ANOVA) revealed a significant between-groups difference regarding the effect of slow breathing on sympathetic activity (p for interaction = 0.01). Comparing sympathetic activity at a respiratory rate of 6/min to MSNA at baseline revealed

similar results (**Figure 1**). Slow breathing as compared to breathing at 15/min or baseline conditions did not influence heart rate and systolic or diastolic blood pressure in either group (see **Tables S1** and **S2** in the online depository).

The effects of slow breathing on baroreflex sensitivity are summarized in **Figure 2**. In both groups, a significant increase in alpha angle values was only observed when comparing slow breathing to breathing at a rate of 15/min (COPD: from 3.3 ± 0.6 ms/mmHg to 5.2 ± 1.1 ms/mmHg, $p = 0.04$; controls: from 7.8 ± 0.9 ms/mmHg to 13.0 ± 2.5 ms/mmHg, $p = 0.042$). Due to this similar trend towards higher baroreflex sensitivity in both groups, no significant interaction effect was detected for either comparison (p for ANOVA = n.s.).

Changes in MSNA induced by slow breathing did not significantly correlate with baseline pO_2 or changes in baroreflex sensitivity (data not shown).

Discussion

Main findings

Our data showing direct evidence of sympathetic overactivation in patients with normoxic COPD extend previous observations in hypoxemic lung disease [3] in that slow breathing acutely reduces sympathetic activity and tends to increase baroreflex sensitivity in COPD patients, thus indicating that slow breathing positively modulates the sympatho-vagal balance that is markedly altered in these patients.

Sympathovagal balance in COPD

In patients with COPD, sympathetic activity was nearly twice as high as in a matched control group of healthy individuals. Importantly, hypoxia was not present in any subject at the time

of study. This extends our previous findings in hypoxic patients [3] to COPD patients without hypoxia.

Our findings indicate that in COPD, sympathetic activation and vagal withdrawal is at least as pronounced as in other chronic conditions such as severe heart failure [9, 18]. Our data are also in line with reports of long-standing heart rate elevation in patients with COPD (for review see [4]). This is further supported by our finding of a significantly decreased baroreflex sensitivity in COPD patients that is in keeping with an earlier study using the phenylephrine test in order to determine baroreceptor sensitivity [7].

It is highly unlikely that inhaled ß-agonists explain our findings, since striking sympathoexitation was found also in patients with restrictive lung disease without any ß-agonist medication [3]. Furthermore intravenous adrenaline (0,3 nmol/kg*min.) caused striking tachycardia but only a mild increase in MSNA from 20 to 23 burst/min [19].

Although slow breathing has a clear effect on the autonomic nervous system in COPD, it does not lead to a normalization of baroreflexes and sympathetic activity in these patients. The data presented here do not prove a causal link between altered baroreflexes and heightened sympathetic activity in COPD. Instead, it is reasonable to suggest that a number of synergistic mechanisms including chemo-, ergo- and lung inflation reflexes contribute to sympathetic activation in COPD [3, 4].

Effects of regular and slow breathing

There are several possible explanations for the effect of slow breathing on sympathoexcitation. Slow breathing may reduce sympathetic activity by enhancing central inhibitory rhythms [20] and, conversely impact on baroreflex sensitivity. Furthermore, activation of the Hering–Breuer reflex due to an increase in tidal volume during slow breathing [21] reduces chemoreflex sensitivity and might thus ameliorate baroreflex function

[11, 21, 22]. Additionally, reducing respiratory rate to 6/min entrains RR interval fluctuations, causing a merging with the respiratory cycle as well as a considerable increase in amplitude relative to blood pressure changes. This may lead to enhanced baroreflex efficiency [9].

Changes in blood gases might contribute but are unlikely to fully explain the observed changes in MSNA and baroreflex sensitivity since the main increase in SaO_2 as well as the main decrease in transcutaneous pCO_2 were observed upon switching from baseline conditions to a respiratory rate of 15/min. During this part of the protocol, no significant changes in MSNA and baroreflex sensitivity were observed. In fact, there was even a small but insignificant increase in MSNA with breathing at 15/min. Thus, SaO_2 increased and $tcPaCO_2$ decreased significantly upon regularization of breathing (15/min) but MSNA did not decrease. Changes in blood gases detected upon slow breathing were minor and only partly significant.

The effect of slow breathing on MSNA was only present in COPD patients. This might be explained by the diverse sympathovagal balance in the two groups. Slow breathing is thus more likely to reduce MSNA in an activated system as compared to a resting system exhibiting basal nerve traffic. Nevertheless, slow breathing has the potential to impact on baroreflex sensitivity in patients and controls alike. Previous studies in patients with chronic heart failure or arterial hypertension found an effect similar to that observed in our study [9, 23].

The impact of slow breathing on muscle sympathetic nerve activity seen in COPD might be attributed to the centrally mediated regularization of the respiratory pattern. However, no significant changes in MSNA were seen upon changing respiratory rate from baseline (i.e. 16-17/min) to 15/min, thereby also regularizing the respiratory cycle.

Interaction of cardiovascular and respiratory control

Taking together this and previous studies [9, 12, 23], it seems that slow breathing induces a generalized attenuation of excitatory pathways regulating respiratory and cardiovascular systems. In this context, mutual interference of these systems in response to alterations affecting only one part is likely to occur since both systems share similar control mechanisms [24]. It has previously been shown that slow breathing reduces chemoreflex activation to hypoxia and hypercapnia in healthy subjects [22]. In the presence of heart failure, a condition known to induce sympathetic activation, slow breathing was associated with a reduction of sympathetic activation as well as a strengthening of inhibitory pathways such as the arterial baroreflex [9, 21]. In addition, this intervention induced an increase in baroreflex and even exercise capacity [9, 12].

The insight in sympathovagal dysbalance as a pathophysiological phenomenon in COPD in concert with the potential to at least partly counteract these changes by slow breathing might pave the way for new treatment strategies which could include multidirectional interventions aimed at the numerous dysfunctions seen in COPD.

Interestingly, pursed-lip breathing reduces respiratory rate and breathlessness in COPD patients at rest and during exercise [25, 26]. Physiotherapy has long been used as an adjunct to pharmacological COPD treatment. We now provide evidence for a possible underlying cause of the beneficial effects of this kind of treatment (which includes training of slow breathing).

Study limitations

Although we observed clear short-term effects of slow breathing, it remains to be assessed whether longer-term practice will lead to stable modifications of cardiovascular and respiratory control.

For unobtrusive registration of the sympathovagal balance, we decided not to evaluate ventilation by mouthpiece. Instead, respiratory inductive plethysmography was used. Although this is the most widely accepted method for noninvasive respiratory measurements, there is as much as 10% deviation between plethysmography and spirometry in patients with lung disease even when using the least-squares calibration technique [27]. On the other hand, highly reliable methods to determine minute ventilation would involve the use of a mouthpiece or a face mask, possibly giving rise to discomfort, alterations in the breathing pattern and an artifactual increase in ventilation [28].

Spontaneous baroreflex sensitivity was assessed in this study. Although more invasive methods such as the phenylephrin method are available, they are also likely to impact on other variables relevant for the question under study. Thus, the less intrusive alpha angle method was preferred since it is an accepted method for measuring baroreflex sensitivity [29].

Due to electrical interference of oxymetry devices with the MSNA signal, oxygen saturation and transcutaneous pCO_2 was only evaluated in a second set of experiments using the same protocol but without registration of MSNA in a limited number of patients. Furthermore, we were unable to control for the effects of pursed lip breathing. Studies using strict methodology to evaluate hemodynamics, blood gases and ventilation will be necessary to better understand the complex effects of slow breathing and pursed lip breathing.

Conclusion

In summary, patients with COPD show sympathetic excitation and depression of the baroreflex. Slow breathing counteracts these changes. Given the negative consequences of sympathetic activation and vagal withdrawal, modulation of the sympatho-vagal balance by slow breathing might have the potential to impact on systemic effects in COPD patients.

Statement of Competing interests

None of the authors has any competing interest to declare.

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References

1. Reid MB. COPD as a muscle disease. *Am J Respir Crit Care Med* 2001;164:1101-2.
2. Wouters EF. Chronic obstructive pulmonary disease. 5: systemic effects of COPD. *Thorax* 2002;57:1067-70.
3. Heindl S, Lehnert M, Criée CP, Hasenfuß G and Andreas S. Marked sympathetic activation in patients with chronic respiratory failure. *Am J Respir Crit Care Med* 2001;164:597-601.
4. Andreas S, Anker SD, Scanlon PD and Somers VK. Neurohumoral activation as a link to systemic manifestation of chronic lung disease. *Chest* 2005;128:3618-3624.
5. Anker SD and Coats AJ. Cardiac cachexia: a syndrome with impaired survival and immune and neuroendocrine activation. *Chest* 1999;115:836-47.
6. Bartels MN, Gonzalez JM, Kim W and De Meersman RE. Oxygen supplementation and cardiac-autonomic modulation in COPD. *Chest* 2000;118:691-6.
7. Patakas D, Louridas G and Kakavelas E. Reduced baroreceptor sensitivity in patients with chronic obstructive pulmonary disease. *Thorax* 1982;37:292-5.
8. Hjalmarsen A, Aasebo U, Aleksandersen G and Jorde R. Cardiovascular responses to tests for autonomic dysfunction in patients with chronic obstructive pulmonary disease with and without continuous long-term oxygen therapy. *J Auton Nerv Syst* 1996;60:169-74.
9. Bernardi L, Porta C, Spicuzza L, Bellwon J, Spadacini G, Frey AW, Yeung LY, Sanderson JE, Pedretti R and Tramarin R. Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. *Circulation* 2002;105:143-5.
10. Dempsey JA, Sheel AW, St Croix CM and Morgan BJ. Respiratory influences on sympathetic vasomotor outflow in humans. *Respir Physiol Neurobiol* 2002;130:3-20.

11. Goso Y, Asanoi H, Ishise H, Kameyama T, Hirai T, Nozawa T, Takashima S, Umeno K and Inoue H. Respiratory modulation of muscle sympathetic nerve activity in patients with chronic heart failure. *Circulation* 2001;104:418-23.

12. Bernardi L, Spadacini G, Bellwon J, Hajric R, Roskamm H and Frey AW. Effect of breathing rate on oxygen saturation and exercise performance in chronic heart failure. *Lancet* 1998;351:1308-11.

13. Wallin BG, Esler M, Dorward P, Eisenhofer G, Ferrier C, Westerman R and Jennings G. Simultaneous measurements of cardiac noradrenaline spillover and sympathetic outflow to skeletal muscle in humans. *J Physiol Lond* 1992;453:45-58.

14. Pauwels RA, Buist AS, Calverley PM, Jenkins CR and Hurd SS. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. NHLBI/WHO Global Initiative for Chronic Obstructive Lung Disease (GOLD) Workshop summary. *Am J Respir Crit Care Med* 2001;163:1256-76.

15. Heindl S, Dodt C, Krahwinkel M, Hasenfuss G and Andreas S. Short term effect of continuous positive airway pressure on muscle sympathetic nerve activity in patients with chronic heart failure. *Heart* 2001;85:185-90.

16. Malliani A, Pagani M, Lombardi F and Cerutti S. Cardiovascular neural regulation explored in the frequency domain. *Circulation* 1991;84:482-92.

17. Rudas L, Crossman AA, Morillo CA, Halliwill JR, Tahvanainen KU, Kuusela TA and Eckberg DL. Human sympathetic and vagal baroreflex responses to sequential nitroprusside and phenylephrine. *Am J Physiol* 1999;276:H1691-8.

18. Andreas S, Reiter H, Luthje L, Delekat A, Grunewald RW, Hasenfuss G and Somers VK. Differential effects of theophylline on sympathetic excitation, hemodynamics, and breathing in congestive heart failure. *Circulation* 2004;110:2157-62.

19. Persson B, Andersson OK, Hjemdahl P, Wysocki M, Agerwall S and Wallin G. Adrenaline infusion in man increases muscle sympathetic nerve activity and noradrenaline overflow to plasma. *J Hypertens* 1989;7:747-56.

20. Naughton MT, Floras JS, Rahman MA, Jamal M and Bradley TD. Respiratory correlates of muscle sympathetic nerve activity in heart failure. *Clin Sci (Lond)* 1998;95:277-85.

21. Bernardi L, Gabutti A, Porta C and Spicuzza L. Slow breathing reduces chemoreflex response to hypoxia and hypercapnia, and increases baroreflex sensitivity. *J Hypertens* 2001;19:2221-9.

22. Spicuzza L, Gabutti A, Porta C, Montano N and Bernardi L. Yoga and chemoreflex response to hypoxia and hypercapnia. *Lancet* 2000;356:1495-6.

23. Joseph CN, Porta C, Casucci G, Casiraghi N, Maffeis M, Rossi M and Bernardi L. Slow breathing improves arterial baroreflex sensitivity and decreases blood pressure in essential hypertension. *Hypertension* 2005;46:714-8.

24. Derchak PA, Sheel AW, Morgan BJ and Dempsey JA. Effects of expiratory muscle work on muscle sympathetic nerve activity. *J Appl Physiol* 2002;92:1539-52.

25. Bianchi R, Gigliotti F, Romagnoli I, Lanini B, Castellani C, Grazzini M and Scano G. Chest wall kinematics and breathlessness during pursed-lip breathing in patients with COPD. *Chest* 2004;125:459-65.

26. Spahija J, de Marchie M and Grassino A. Effects of imposed pursed-lips breathing on respiratory mechanics and dyspnea at rest and during exercise in COPD. *Chest* 2005;128:640-50.

27. Tobin MJ, Jenouri G, Lind B, Watson H, Schneider A and Sackner MA. Validation of respiratory inductive plethysmography in patients with pulmonary disease. *Chest* 1983;83:615-20.

28. Askanazi J, Silverberg PA, Foster RJ, Hyman AI, Milic-Emili J and Kinney JM. Effects of respiratory apparatus on breathing pattern. *J Appl Physiol* 1980;48:577-80.

29. Davies LC, Francis D, Jurak P, Kara T, Piepoli M and Coats AJ. Reproducibility of methods for assessing baroreflex sensitivity in normal controls and in patients with chronic heart failure. *Clin Sci (Lond)* 1999;97:515-22.

Table

Table. Baseline characteristics of study subjects.			
	COPD (n = 15)	Control (n = 15)	p value
Age, years	60.9 ± 1.4	60.7 ± 1.4	0.919
Height, m	1.71 ± 0.02	1.75 ± 0.03	0.254
Weight, kg	78.7 ± 3.1	81.1 ± 2.6	0.553
Body mass index, kg/m^2	27.0 ± 1.1	26.5 ± 0.9	0.735
FEV_1, % predicted	46.4 ± 3.7	101.4 ± 2.5	<0.001
FEV_1/Vital capacity	53.5 ± 2.8	79.0 ± 1.0	<0.001
Vital capacity, % predicted	63.1 ± 4.1	95.2 ± 3.0	<0.001
RV/TLC	47.3 ± 3.2	35.1 ± 2.9	0.017
p0.1, kPa	0.39 ± 0.05	0.11 ± 0.03	<0.001
pimax, kPa	5.64 ± 0.64	8.41 ± 0.95	0.026
arterial pH	7.38 ± 0.01	7.38 ± 0.01	0.797
arterial pCO_2	42.0 ± 0.91	39.1 ± 1.05	0.048
arterial pO_2	76.5 ± 2.3	82.5 ± 2.8	0.112
arterial O_2 saturation	94.5 ± 0.5	95.3 ± 0.5	0.284
systolic blood pressure, mmHg	127.5 ± 8.2	135.6 ± 7.6	0.476
diastolic blood pressure, mmHg	62.8 ± 3.5	68.7 ± 3.4	0.244
Heart rate, min^{-1}	79.0 ± 3.2	69.7 ± 1.7	0.016
Respiratory rate, min^{-1}	16.2 ± 1.1	16.9 ± 0.7	0.603
Epinephrine, ng/l	26.6 ± 3.9	27.9 ± 4.7	0.844
Norepinephrine, ng/l	222.6 ± 16.0	218.0 ± 22.9	0.869
FEV_1, forced exspiratory volume in 1 second; RV, residual volume; TLC, total lung capacity. p0.1, mouth occlusion pressure at 0.1 seconds; pimax, maximal inspiratory pressure.			

Figure legends

Figure 1: Effect of regular and slow breathing on muscle sympathetic nerve activity (MSNA) in COPD patients (n = 15) and healthy control subjects (n = 15). * $p < 0.01$; † $p < 0.001$

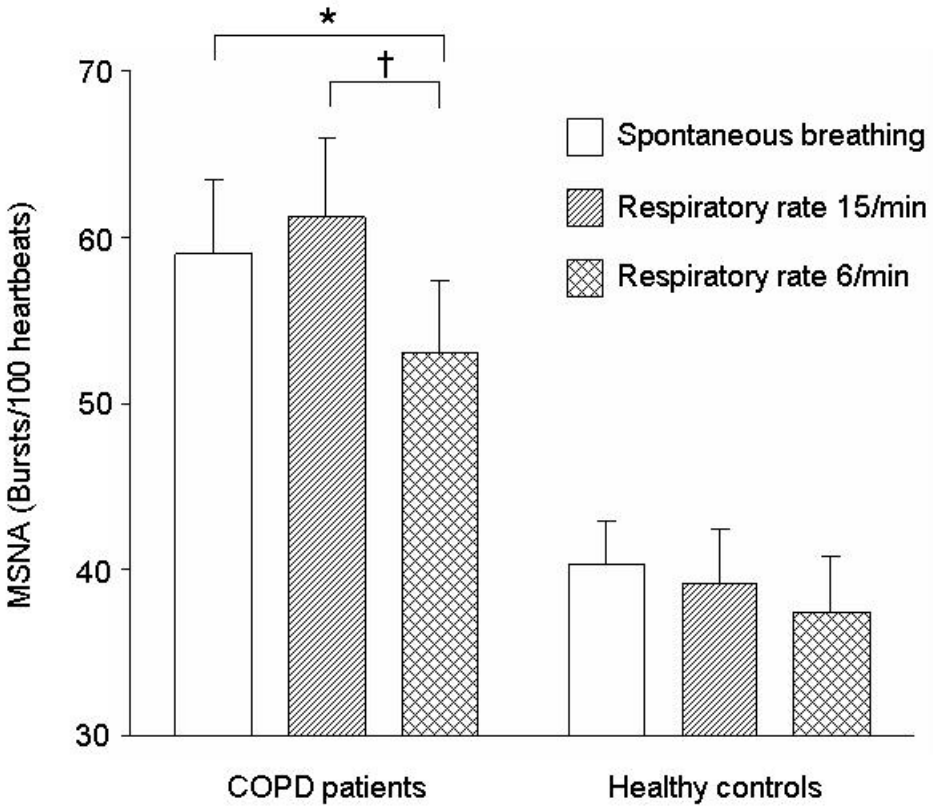

Figure 2: Effect of regular and slow breathing on baroreflex sensitivity in COPD patients (n = 12) and healthy control subjects (n = 12). ‡ $p < 0.05$

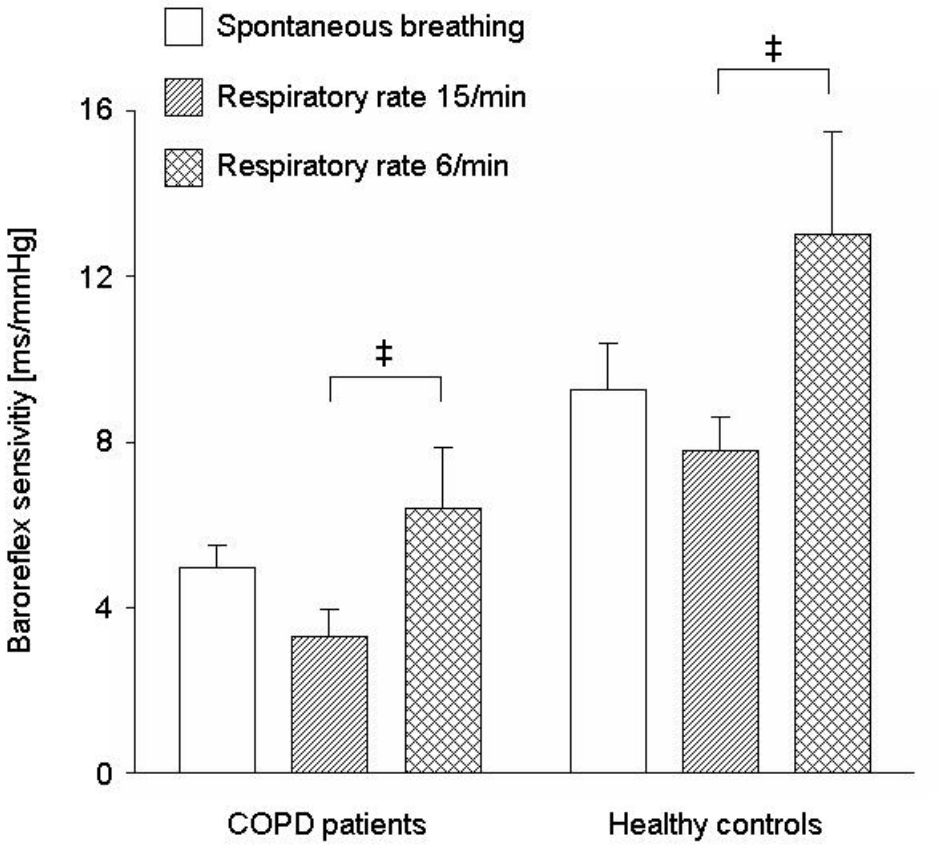

Figure 3: Exemplary display of the effect of slow breathing on muscle sympathetic nerve activity (MSNA, integrated data) and blood pressure in a healthy control subject and a COPD patient.