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Inspiratory resistive loading does not increase sympathetic tone in COPD

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Summary
Objectives: Neurohumoral activation has been shown to be present in patients with chronic obstructive pulmonary disease (COPD). The increase in respiratory muscle work might be responsible for the observed elevation of sympathetic tone via a respiratory muscle ergoreflex in these patients. The aim of this study is to investigate whether moderately increasing inspiratory resistive loading will impact on sympathetic activity in healthy subjects and COPD patients.
Methods: Efferent muscle sympathetic nerve activity, blood pressure, heart rate and respiratory movements were continuously measured in 15 patients and 15 healthy control subjects. In order to increase work of breathing as evaluated by the tension-time index, inspiratory resistive loading was performed while patients were breathing through a spirometer.
Results: At baseline, sympathetic nerve activity was significantly elevated in patients. Resistive loading increased work of breathing (tension-time index) by roughly 110% (COPD) and 130% (controls) but did not significantly alter blood gases or sympathetic activity in either group.
Conclusions: Doubling the work of breathing does not affect sympathetic activation in COPD patients or healthy control subjects. Thus in COPD the respiratory muscle ergoreflex does not seem to play a major role in sympathoexcitation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a major cause of death and disability worldwide. In COPD, numerous extrapulmonary abnormalities are present.

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These include systemic inflammation, cachexia and skeletal muscle dysfunction. COPD has thus been called a muscle[1] and a systemic disease.[2,3] Recent data demonstrate that hypoxemic COPD causes marked neurohumoral activation.[4] Notably, heightened sympathetic tone has also been noted in patients suffering from congestive heart failure.[5] Given the similarities between pathophysiological findings in heart failure and COPD[6] and considering the negative systemic consequences of neurohumoral activation, it is conceivable that in the context of COPD, vegetative dysfunction may well have direct implications for inflammation, cachexia and skeletal muscle dysfunction.[7]

Currently, little is known about the cause of profound sympathetic activation in patients with COPD. It has recently been shown that reducing respiratory rate results in an acute decrease in sympathetic activity in COPD patients but not in healthy controls.[8] However, work of breathing was not assessed in that study.

Alterations in peripheral skeletal muscles and diaphragm function are present and are related to exercise limitation and severity of disease in patients with COPD.[1,9,10] In COPD the diaphragm is characterized by oxidative stress, sarcomeric injury and ultimately by contractile protein wasting.[11,12] Similar to peripheral skeletal muscles, the diaphragm contains unmylenated type III and IV sensory nerve fibres.[13,14] These muscle afferents constitute the ergoreflex and activate the sympathetic nervous system at rest[14,15] and more noticeably during exercise.[13,16] Indeed, studies in healthy men using microneurographic recordings revealed that high-intensity contractions of expiratory muscles to the point of task failure cause a time-dependent sympathoexcitation.[17] In COPD patients, work of breathing is increased even at rest.[18]

We therefore decided to evaluate whether moderate inspiratory loading as present in COPD impacts on sympathetic activation in COPD patients and in healthy controls. To this end, sympathetic activity was measured using microneurographic recordings of efferent muscle sympathetic nerve activity (MSNA) in the peroneal nerve.[19]

Methods

Subjects

Non-smoking, normoxic individuals aged 30-80 years with stable sinus rhythm and a diagnosis of COPD with a $FEV_1 \leq 60\%$ predicted who were on medical treatment according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guideline[20] were eligible for participation in the study. General exclusion criteria were hypercapnia ($PaCO_2 > 45$ mm Hg) based 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. Most patients and controls had also participated in a previous investigation.[8]

Patients were asked not to take any diuretic drugs before the measurements were completed. Informed written consent was obtained from all patients and control subjects.

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 min, after which patients were asked to breathe through a mouthpiece. Work of breathing was increased every four minutes by inserting perforated plates to increase inspiratory resistance. The patients breathed room air through a mouthpiece connected to an occlusion valve. Three different resistors were used (2.0, 4.5 and 10.0 hPa/l/s); flow-pressure curves of these resistors were found to be linear (see Fig. 1).

Simultaneous measurement of sympathetic activity and blood gases would have caused an electrical interference leading to decreased MSNA signal quality. Thus, in order to determine SaO_2 (Oxycount®, Andos MCC Karlsruhe, Germany) and transcutaneous pCO_2 (Tosca®, Linde Medical Sensors, Basel, Switzerland) during inspiratory loading, the protocol was repeated in six COPD patients and six healthy controls belonging to the original study population. These subjects showed no significant differences in baseline parameters as compared to the other subjects.

In-vivo measurements

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.[4,21] This method provides not only

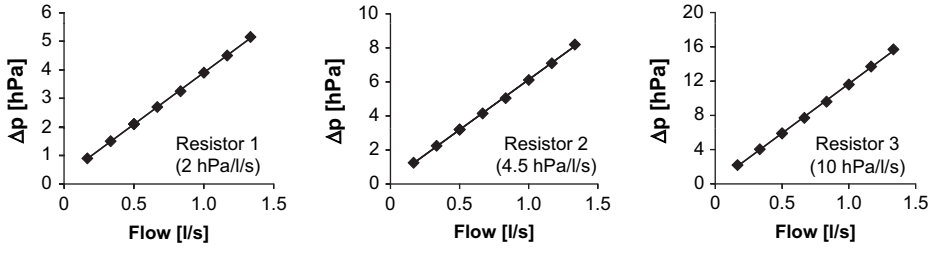

Figure 1 Flow-pressure curves of the three resistors used to increase work of breathing.