

Bronchodilator effect on maximal breath-hold time in patients with obstructive lung disease*

Efeito do broncodilatador no tempo de apneia voluntária máxima em pacientes com distúrbios ventilatórios obstrutivos

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Abstract

Objective: To identify the role of bronchodilators in the maximal breath-hold time in patients with obstructive lung disease (OLD). **Methods:** We conducted a case-control study including patients with OLD and a control group. Spirometric tests were performed prior to and after the use of a bronchodilator, as were breath-hold tests, using an electronic microprocessor and a pneumotachograph as a flow transducer. Respiratory flow curves were displayed in real time on a portable computer. The maximal breath-hold times at end-inspiratory volume and at end-expiratory volume ($BHT_{max} V_{EI}$ and $BHT_{max} V_{EE}$, respectively) were determined from the acquired signal. **Results:** A total of 35 patients with OLD and 16 controls were included. Prior to the use of a bronchodilator, the $BHT_{max} V_{EI}$ was significantly lower in the OLD group than in the control group (22.27 ± 11.81 s vs. 31.45 ± 15.73 s; $p = 0.025$), although there was no significant difference between the two groups in terms of the post-bronchodilator values (24.94 ± 12.89 s vs. 31.67 ± 17.53 s). In contrast, $BHT_{max} V_{EE}$ values were significantly lower in the OLD group than in the control group, in the pre- and post-bronchodilator tests (16.88 ± 6.58 s vs. 22.09 ± 7.95 s; $p = 0.017$; and 21.22 ± 9.37 s vs. 28.53 ± 12.46 s; $p = 0.024$, respectively). **Conclusions:** Our results provide additional evidence of the clinical usefulness of the breath-hold test in the assessment of pulmonary function and add to the existing knowledge regarding the role of the bronchodilator in this test.

Keywords: Respiratory function tests; Pulmonary disease, chronic obstructive; Bronchodilator agents; Apnea.

Resumo

Objetivo: Identificar o papel do broncodilatador no tempo de apneia voluntária máxima em pacientes com distúrbios ventilatórios obstrutivos (DVOs). **Métodos:** Estudo caso-controle incluindo pacientes com DVOs e grupo controle. Foram realizadas espirometrias antes e após o uso de broncodilatador, assim como testes de apneia respiratória, utilizando-se um microprocessador eletrônico e um pneumotacógrafo como transdutor de fluxo. As curvas de fluxo respiratório foram exibidas em tempo real em um computador portátil, e os tempos de apneia voluntária inspiratória e expiratória máximos (TAVIM e TAVEM, respectivamente) foram determinados a partir do sinal adquirido. **Resultados:** Um total de 35 pacientes com DVOs e 16 controles foram incluídos no estudo. O TAVIM sem o uso de broncodilatador foi significativamente menor no grupo DVO que no grupo controle ($22,27 \pm 11,81$ s vs. $31,45 \pm 15,73$; $p = 0,025$), mas essa diferença não foi significativa após o uso de broncodilatador ($24,94 \pm 12,89$ s vs. $31,67 \pm 17,53$ s). Os valores de TAVEM foram significativamente menores no grupo DVO que no grupo controle antes ($16,88 \pm 6,58$ s vs. $22,09 \pm 7,95$ s; $p = 0,017$) e após o uso de broncodilatador ($21,22 \pm 9,37$ s vs. $28,53 \pm 12,46$ s; $p = 0,024$). **Conclusões:** Estes resultados fornecem uma evidência adicional da utilidade clínica do teste de apneia na avaliação da função pulmonar e do papel do broncodilatador nesse teste.

Descritores: Testes de função respiratória; Doença pulmonar obstrutiva crônica; Broncodilatadores; Apneia.

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Introduction

The World Health Organization estimates that COPD kills more than 2.75 million people each year. Every 10 seconds, one person dies from COPD. According to the World Health Organization, COPD is, together with AIDS/HIV, the fourth leading cause of death worldwide, after heart diseases, cerebrovascular diseases, and pneumonia. In Brazil, approximately 40,000 people die from COPD each year, and approximately 7 million Brazilians have the disease. For the Brazilian Unified Health Care System, COPD is the respiratory disease that has the highest cost.⁽¹⁾

Patients with COPD present with various functional changes, the most typical finding being a persistent reduction in forced expiratory flow. Clinical trials examining the reversibility of obstructive lung disease (OLD) in COPD are usually based on expiratory flow measurements and their variation after the use of inhaled bronchodilators, FEV₁ being the parameter that is most commonly used in order to characterize airflow limitation in OLD.⁽²⁾ It is convenient to think of FEV₁ as the mean flow during the first second of FVC. In addition, FEV₁ is used in order to determine the degree of airflow obstruction (mild, moderate, or severe) in COPD patients, as well as being used in the functional follow-up of such patients.⁽³⁾

Other measurements, taken when tracing a volume-time curve for FVC, are also useful in grading OLD. The transition from functionally normal airways to mildly obstructed airways is generally gradual.^(2,3)

When patients with airflow obstruction are tested after the use of placebo or without active medication, limits of variation in functional parameters are established. A statistically significant response (i.e., beyond random variability) is characterized by such limits being exceeded after bronchodilator use. Increases of 0.2 L or more in FEV₁ and 0.35 L or more in FVC are widely used in order to characterize that response.^(2,3)

More than two centuries have passed since the classical experiment conducted by Valsava in 1740 showed the easily recognizable effect of sustained forced expiratory maneuvers on HR. Nearly one hundred years later, in 1838, Johannes Müller complemented that experiment by demonstrating the effects of forced inspiratory

maneuvers, under similar conditions, on HR. Those two experiments were early indicators of the close relationship of the cardiorespiratory mechanism in health and disease.^(4,5)

Apnea is an unstable state, changes occurring in numerous interrelated variables. The breath-hold test is simple and rapid. It consists of determining how long individuals can hold their breath. Maximal breath-hold time (BHT_{max}) varies from individual to individual and depends on chemical and nonchemical stimuli.^(6,7)

It has been demonstrated that BHT is reduced by something that increases the response of diaphragmatic afferents (a tonic activity of the diaphragm and, possibly, arterial hypoxia and hypercapnia) or that increases central respiratory rhythm (arterial hypoxia or hypercapnia, decreased lung volume, or increased metabolic rate).⁽⁸⁾

The breath-hold test was tested in certain clinical settings and proved to be extremely useful clinically.⁽⁸⁻¹⁰⁾ The test can be used both as a screening test, raising the suspicion of OLD, and as a lung function parameter, similar to FEV₁ and FVC.

A potential clinical and functional respiratory test, BHT can complement clinical examination, raising the suspicion of pathophysiological abnormalities, such as lung hyperinflation.

The objective of the present study was to evaluate the effect of bronchodilator use on the BHT_{max} in patients with OLD.

Methods

This was a prospective case-control study. The participants were over 18 years of age and had been referred to the Pulmonary Physiology Clinic of the Pulmonology Department of the *Hospital de Clínicas de Porto Alegre* (HCPA, Porto Alegre Hospital de Clínicas), in Porto Alegre, Brazil, for spirometry. Patients with OLD constituted the study group, whereas those with normal spirometry results constituted the control group.

The participants were interviewed, data having been collected with a standardized questionnaire comprising questions regarding demographic data, smoking habit, and comorbidities. The study protocol was approved by the HCPA Research Ethics Committee, and all of the participants gave written informed consent.

Patients who presented with severe coronary artery disease, cardiac arrhythmias, acute myocardial infarction, traumatic brain injury, glaucoma, hemoptysis, unstable angina, retinal detachment, hypertension, or pulmonary edema were excluded from the present study, as were pregnant women.⁽¹⁰⁾

Pulmonary function was evaluated with a MasterScreen Body spirometer (Jaeger, Würzburg, Germany), in accordance with the American Thoracic Society/European Respiratory Society guidelines^(10,11) and previously published reference values.⁽¹²⁻¹⁶⁾

In order to determine the BHT_{max} at end-inspiratory volume ($BHT_{max} V_{EI}$), we instructed the participants to inhale deeply three times (with a mouthpiece and a nose clip); at the end of the third maximal inspiratory maneuver, the participants were instructed to hold their breath for as long as they could. In order to determine the BHT_{max} at end-expiratory volume ($BHT_{max} V_{EE}$), we instructed the participants to inhale and exhale deeply (under the same conditions as those described above) three times and then hold their breath for as long as they could. Each maneuver was performed three times.

Spirometry was performed prior to and after the use of a bronchodilator in order to determine the effect of the bronchodilator on the $BHT_{max} V_{EI}$ and $BHT_{max} V_{EE}$.

The respiratory flow and apneas were monitored by a pneumotachograph (Hans Rudolph, Kansas City, MO, USA). The pneumotachograph was originally described by Fleisch in 1925; since then, the device has undergone various modifications in an attempt to improve the original concept. The pneumotachograph can measure the respiratory flow and is usually used in order to measure gas flow rates in ICU monitors, respirators, and ventilators.^(3,12) The pneumotachograph design allows a pressure variation that is proportional to the air flow inside the device. The pressure variation is converted into an electrical signal by means of a solid-state pressure transducer. The electrical signal is then conditioned and digitized in order to be serially transmitted to a portable computer. A specially designed program allowed us to visualize the respiratory flow curves in real time. The curves were stored for subsequent analyses. The different times ($BHT_{max} V_{EI}$,

$BHT_{max} V_{EE}$, and BHT) were automatically quantified (in seconds) from selected segments of the flow curve.

The system is heated in order to prevent condensation within the capillary tubes, which can result in reading errors. In the capillary tubes there is a stainless steel screen that is heated and provides resistance; a mouthpiece with a disposable filter was attached to the device in order to avert the impact of particulate matter and aid in creating a laminar flow.^(3,12)

The statistical analysis was performed with the Statistical Package for the Social Sciences, version 18.0 (SPSS Inc., Chicago, IL, USA). The data were expressed as frequencies, means \pm SD, or medians (interquartile ranges). Pearson's correlation coefficient was used in order to determine the correlations among the variables $BHT_{max} V_{EI}$, $BHT_{max} V_{EE}$, and FEV₁/FVC ratio prior to and after bronchodilator use. In order to identify correlations (minimum $r = 0.60$) among those variables, with a power of 80% and a significance of 5%, 19 patients were required. The level of significance was set at $p < 0.05$ for all analyses.

Results

Between May and November of 2010, 51 individuals (35 patients with OLD and 16 controls) were included in the present study. In the OLD group, the physician who requested spirometry diagnosed the following underlying diseases: asthma, in 17 (48.6%); COPD, in 11 (31.4%); dyspnea, in 3 (8.57%); pulmonary nodules, in 2 (5.71%); and preoperative period of vascular surgery, in 2 (5.71%). Of the patients with OLD, 6 (17.14%) were classified as having incipient OLD, 13 (37.14%) were classified as having mild OLD, 10 (28.57%) were classified as having moderate OLD, and 6 (17.14%) were classified as having severe OLD.⁽¹⁷⁾ Table 1 shows the general characteristics of the study population.

The mean age of OLD group patients was 57.4 ± 13.1 years, whereas that of control group patients was 44.6 ± 16.8 years ($p = 0.05$). The prevalence of smoking was higher in the OLD group than in the control group (62.9% vs. 31.3%; $p = 0.004$). Pre-bronchodilator $BHT_{max} V_{EI}$ was shorter in the OLD group than in the control group (22.27 ± 11.81 s vs. 31.45 ± 15.73 s; $p = 0.025$). There were no statistically significant

Table 1 – General characteristics of the study population.^a

| Parameter | Group | | p |
|--|---------------|---------------|----------|
| | OLD | Control | |
| | (n = 35) | (n = 16) | |
| Age, years | 57.40 ± 13.13 | 44.56 ± 16.79 | 0.05 |
| FVC before, L | 2.81 ± 0.93 | 3.51 ± 0.81 | 0.012 |
| FVC after, L | 3.04 ± 0.99 | 3.53 ± 0.74 | 0.088 |
| FEV ₁ before, L | 1.74 ± 0.83 | 3.01 ± 0.71 | < 0.0001 |
| FEV ₁ after, L | 1.95 ± 0.88 | 3.12 ± 0.66 | < 0.0001 |
| BHT _{max} V _{EI} before, s | 22.27 ± 11.81 | 31.46 ± 15.73 | 0.025 |
| BHT _{max} V _{EI} after, s | 24.94 ± 12.89 | 31.67 ± 17.54 | 0.130 |
| BHT _{max} V _{EE} before, s | 16.88 ± 6.58 | 22.09 ± 7.95 | 0.017 |
| BHT _{max} V _{EE} after, s | 21.22 ± 9.37 | 28.54 ± 12.47 | 0.024 |

OLD: obstructive lung disease; before: before bronchodilator use; after: after bronchodilator use; BHT_{max} V_{EI}: maximal breath-hold time at end-inspiratory volume; and BHT_{max} V_{EE}: maximal breath-hold time at end-expiratory volume. ^aValues expressed as mean ± SD.

differences between the two groups in terms of the post-bronchodilator BHT_{max} V_{EI}.

Pre-bronchodilator BHT_{max} V_{EE} values were significantly lower in the OLD group than in the control group (16.88 ± 6.58 s vs. 22.09 ± 7.95 s; p = 0.017), as were post-bronchodilator BHT_{max} V_{EE} values (21.22 ± 9.37 s vs. 28.54 ± 12.46 s; p = 0.024).

In the OLD group, we found significant, positive bivariate correlations between pre-bronchodilator BHT_{max} V_{EI} and the following: pre-bronchodilator FEV₁ in L (r = 0.383; p = 0.023); post-bronchodilator FEV₁ in L (r = 0.362; p = 0.033); pre-bronchodilator FVC in L (r = 0.476; p = 0.004); and post-bronchodilator FVC in L (r = 0.486; p = 0.004). Post-bronchodilator BHT_{max} V_{EI} did not correlate significantly with any of the pulmonary function parameters in the OLD group. Neither pre- nor post-bronchodilator BHT_{max} V_{EE} correlated significantly with any of the pulmonary function parameters in either group (Table 2).

Discussion

The objective of the present case-control study was to evaluate the effect of bronchodilator use on the BHT_{max} in patients with OLD and in normal individuals. We demonstrated that pre-bronchodilator BHT_{max} V_{EI} and BHT_{max} V_{EE} values were lower in the OLD group than in the control group. However, after bronchodilator use, only BHT_{max} V_{EE} values were significantly lower in the OLD group. In addition, after bronchodilator use, neither BHT_{max} V_{EI} nor BHT_{max} V_{EE} correlated significantly with any of the pulmonary function parameters (Figures 1 and 2).

The breath-hold test is one of many methods used in order to induce a sensation of dyspnea and provide information regarding the onset of and resistance to the sensation of dyspnea. In conscious individuals, immediately after the onset of apnea in functional residual capacity, there is a period of 20–30 s in which no particular respiratory sensation is experienced. That period

Table 2 – Correlations between the maximal breath-hold time at end-inspiratory volume and spirometric parameters.*

| Parameter | Group | | | | | | | |
|----------------------------|--|-------|---|-------|--|-------|---|-------|
| | OLD | | | | Control | | | |
| | (n = 35) | | | | (n = 16) | | | |
| | BHT _{max} V _{EI} before, s | | BHT _{max} V _{EI} after, s | | BHT _{max} V _{EI} before, s | | BHT _{max} V _{EI} after, s | |
| r | p | r | p | r | p | r | p | |
| FVC before, L | 0.476 | 0.004 | 0.271 | 0.115 | 0.480 | 0.060 | 0.321 | 0.225 |
| FVC after, L | 0.486 | 0.003 | 0.265 | 0.123 | 0.437 | 0.091 | 0.268 | 0.315 |
| FEV ₁ before, L | 0.383 | 0.023 | 0.257 | 0.136 | 0.441 | 0.087 | 0.315 | 0.235 |
| FEV ₁ after, L | 0.362 | 0.033 | 0.233 | 0.178 | 0.421 | 0.105 | 0.294 | 0.269 |

OLD: obstructive lung disease; BHT_{max} V_{EI}: maximal breath-hold time at end-inspiratory volume; before: before bronchodilator use; and after: after bronchodilator use. *Pearson's correlation coefficient.

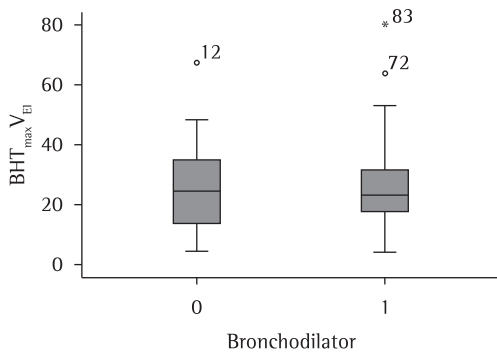


Figure 1 – Maximal breath-hold time at end-inspiratory volume ($BHT_{max} V_{EI}$) prior to bronchodilator use (0) and after bronchodilator use (1).

ends with the onset of dyspnea and is followed by a progressive increase in the intensity of dyspnea until apnea is interrupted. By measuring the apnea period, we can obtain information regarding the threshold of the sensation of dyspnea. Therefore, the measurement of the entire apnea period provides a yardstick of the behavior of the tolerance limit for the sensation of dyspnea.⁽¹⁷⁾

The breath-hold test has previously been used in patients with panic disorder; in addition, the test has been used in combination with the Borg scale and the FEV_1/FVC ratio in order to evaluate the perception of dyspnea in asthma patients, having detected a low perception of dyspnea in those patients.⁽¹⁸⁾ A recent study⁽²⁾ demonstrated another possible contribution of the breath-hold test. In individuals who smoke, are obese, or both, the breath-hold test reveals

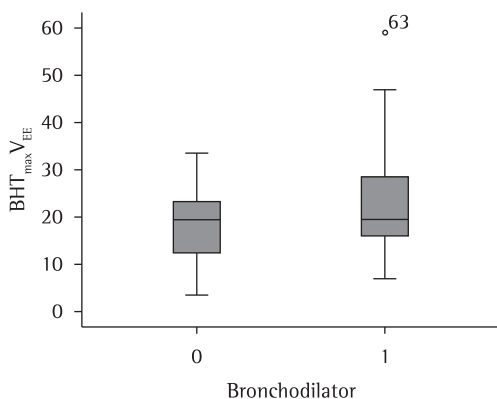


Figure 2 – Maximal breath-hold time at end-expiratory volume ($BHT_{max} V_{EE}$) prior to bronchodilator use (0) and after bronchodilator use (1).

pulmonary abnormalities, even in cases in which spirometry results are normal.⁽²⁾

In the present study, pre- and post-bronchodilator $BHT_{max} V_{EE}$ values were significantly lower in the OLD group than in the control group. Nevertheless, in both groups, $BHT_{max} V_{EE}$ values were found to improve significantly after bronchodilator use. Although a previous study suggested that the breath-hold test was useless as a pulmonary function test,⁽¹⁹⁾ various studies have shown that the breath-hold test can play a role in the evaluation of dyspnea and that bronchodilator use increases $BHT_{max} V_{EE}$ values.^(8-10,20-22)

We found no significant differences between the OLD group and the control group in terms of post-bronchodilator $BHT_{max} V_{EI}$. In the OLD group, bronchodilator use increased the $BHT_{max} V_{EI}$, the difference between the two groups having become less than significant. In a previous study, in which the $BHT_{max} V_{EI}$ was sequentially measured in the postoperative period, the authors reported that the test was easy to perform, was well accepted by patients, and was an interesting tool to be used in the clinical follow-up of patients in the postoperative period, having aided in detecting complications during that period.⁽²²⁻²⁶⁾ However, that study did not evaluate the role of bronchodilator use in the $BHT_{max} V_{EI}$.

Our study has some limitations. First, the investigation was conducted in a single center. Second, our study sample was small. Despite those limitations, our results provide additional evidence of the effect of bronchodilator use on the $BHT_{max} V_{EI}$ and $BHT_{max} V_{EE}$.

In conclusion, we found that pre- and post-bronchodilator $BHT_{max} V_{EI}$ and $BHT_{max} V_{EE}$ values were lower in the OLD group than in the control group. However, after bronchodilator use, only $BHT_{max} V_{EE}$ values were significantly lower in the OLD group. The breath-hold test can aid in recognizing severe pulmonary changes, as well as in promoting a more effective behavioral intervention. Post-bronchodilator $BHT_{max} V_{EI}$ and $BHT_{max} V_{EE}$ values should be interpreted with caution, given that they can be significantly different from pre-bronchodilator values. Further studies are needed in order to confirm the usefulness of the breath-hold test and the effect of bronchodilator use, particularly as a screening tool for the evaluation of dyspnea.

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